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PEPTIC ULCER OF THE ESOPHAGUS.*

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Peptic ulcer of the esophagus, which closely resembles a similar affection in the stomach and duodenum, occurs most frequently in the lower third of the esophagus. Though this condition is rare, it occurs sufficiently often to be of clinical interest; however, but little attention has been directed to it, especially in this country.

Tilleston[1] classifies all other forms of ulcerations of the esophagus into the following groups, which he considers must be excluded before the diagnosis of peptic ulcer is made: (1) carcinomatous; (2) due to the action of corrosive substances; (3) due to foreign bodies; (4) occurring in the course of acute infectious diseases; (5) decubitus; (6) due to aneurysm; (7) catarrhal; (8) due to traction diverticula; (9) tuberculous; (10) syphilitic; (11) varicose; (12) due to thrush.

These forms of ulceration need not be considered here. The recognition of peptic ulcer of the esophagus has been a matter of comparatively recent date, though isolated cases have been reported as far back as 1839. Von Hacker and Lotheissen,[2] however, note that many of these were so indefinitely described that the diagnosis of peptic ulcer remains doubtful.

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The first case to be described in literature was that reported by Albers[3] in 1839. This was followed by Valleix,[4] 1844; Reeves,[5] 1853; Flower,[6] 1853; Vigla,[7] 1855; Part,[8] 1857; Trier,[9] 1864; Eras,[10] 1866; Knott,[11] 1878. In all of these cases, attention was called to the similarity of the lesion to that observed in perforating gastric ulcer. However, Zenker[12] was convinced that the ulceration in these cases was due to carcinoma or perforated traction diverticula or to foreign bodies, or that other causes existed other than actual peptic ulcer.

The 3 first cases which were histologically proven were described by Quincke,[13] in 1879, and this author deserves the credit of having placed this affection upon a definite pathologic and clinical basis.

Since this period, von Hacker and Lotheissen[2] have collected 91 cases in all. Of these, however, but a small number have been definitely proven by autopsy or by histologic studies. In some of these cases, scars were noted which on further investigation were observed to be due to peptic ulcer. A few instances of peptic ulcer of the esophagus have been described in children. Spiegelberg[14] and Meier[15] observed fatal hemorrhages in 2 infants, aged five and six years, and Dorn[16] reports a similar outcome in a female, aged five months, due to an ulcer situated just above the cardia. Zuppinger[17] has reported a perforation due to peptic ulcer in a child aged eight years which was fatal. Meulengracht[18] described a peptic ulcer of the esophagus in a female, aged two and three-quarters years, which was associated with dilatation.

Pathology. Peptic ulcers of the esophagus are usually observed in the lower third of the esophagus, though occasionally they are located higher. When occurring high they are usually produced by extension from below though they may be due to unusual causes, such as trauma, traction diverticula or to tuberculosis.

When situated low near the cardia they rarely extend down into the stomach. In six instances collected by Tilleston[1] all of which came to autopsy, the adjacent wall of the stomach was likewise invaded; however, in these cases the cardia was found to be the primary seat of involvement, the ulcer extending directly up into the esophagus. This observation has been confirmed by Eversmann,[19] Fraenkel[20] and others.

The size of ulcers of the esophagus varies greatly. They are often small and may again be 8 to 10 cm. in length as has been described by Quincke[13] and Zahn.[21] They are usually single, occasionally multiple. The small ulcers are ordinarily round or oval, while the larger ones are irregular in appearance. The large cylindrical ulcers are due in some instances to a confluence of smaller ones (Reher[22]).

The right posterolateral wall of the esophagus is usually most frequently involved in this disease. In the instances collected by Tilleston,[1] the ulcer was found in the anterior wall twice, in the posterior wall three times, on the left side twice on the right three times.

Peptic ulcer of the esophagus may be very superficial, appearing only as hemorrhagic erosions or simple mucosal ulcers. On the other hand, they may be extremely deep; and, as in ulcer of the stomach, bloodvessels may become eroded leading to hemorrhage, or perforation may take place or adhesions to neighboring organs may form.

In the superficial ulcers the edges are clean cut, presenting a reddened granular base. In those of long duration, a punched-out appearance is noted with a funnel-shaped base, the base often being smooth with undermined edges. The surrounding membrane is usually normal in appearance. These ulcers, therefore, resemble in many respects ulcer of the stomach and duodenum. It is interesting to note that when perforations do occur they are apt to take place into the abdominal or lesser peritoneal cavity. Perforations of this type have been described by Winkler,[23] Huwald,[24] Sencert.[25] Perforations may, however, take place instead into the periesophageal connective tissue, pericardium or right or left pleura and gangrene of the lung with pyopneumothorax may result or the aorta may become involved.

As in ulcer of the stomach, healing usually occurs with the production of cicatrices. In the small ulcers, but slight scars occur producing but a miminal degree of puckering. In large ones, contraction takes place with the formation of stenosis. This is usually circumscribed and can be easily recognized by means of fluoroscopy or esophagoscopy. It can be readily dilated but hemorrhage is easily produced; a condition described by Guisez[26] as characteristic of peptic ulcer of the esophagus.

According to Tilleston,[1] scars occur in 25 per cent of the cases. Sencert[25] considers, however, that healing is far more common than is realized, inasmuch as only severe types of the disease have thus far been recognized. This is probably true, inasmuch as in addition to the presence of the ulcer of the esophagus an identical condition often occurs simultaneously in the stomach and duodenum and the esophageal lesion is thus apt to be overlooked. Microscopically, the usual characteristic inflammatory infiltration without evidence of tuberculosis or cancer is noted, together with slight hemorrhages and occasionally thrombosed arteries. Stoerk was the first to observe in a case of Fraenkel's in Nothnagel's Clinic, glands at the edge of the ulcer, which in all respects resembled those of the stomach. This observation was confirmed in a case noted by Tilleston.[1] Schaffer,[27] however, claims that glands of this type may exist in the normal esophagus at times. The examination of the stricture area of the wall of the esophagus reveals sclerotic connective tissue, which invades all the layers of the esophagus and which also surrounds the markedly hypertrophied muscle fibers.

According to von Hacker and Lotheissen,[2] in 17 instances these ulcers were detected accidentally at autopsy, the immediate cause of death being peritoneal cancer, Bright's disease, gall-bladder

perforation and perforating gastric ulcer. Difficulty may arise in determining the exact etiology when only a cicatrix remains. The similarity to an apparently healed superficial carcinomatous ulcer must be considered or to an ulcer produced by a foreign body or even to other less frequent conditions as perforations from without or perforating traction diverticula.

Etiology The etiology of peptic ulcer of the esophagus is in every respect similar to that of the stomach and duodenum, and, therefore, requires no further discussion here. In order, however, that this affection may occur it is necessary that the cardia remain patent, so that the regurgitated acid gastric secretion may continue its corrosive effect upon the localized diseased area in the mucous membrane of the esophagus. Diseases in which vomiting or regurgitation of food occur therefore play an important rôle in its etiology.

Attention has been called by Tilleston,[1] von Hacker and Lotheissen[2] and others to the occurrence of this affection associated with stenosis of the pylorus and gastric dilatation which may produce a relative insufficiency of the cardia allowing the continued regurgitation of the acid secretion. This occurred in 23 per cent of the cases collected by Tilleston. As a further proof of the truth of this explanation, von Hacker cites an instance of pyloric stenosis associated with peptic ulcer of the esophagus in which healing of the esophageal lesion was brought about by means of gastroenterostomy.

That regurgitation of the acid gastric juice cannot alone produce ulceration of the esophagus is evidenced by the fact that in many instances of the most aggravated types of pyloric stenosis, this lesion is not produced. The relation of the gastric acidity to esophageal ulceration has been noted by Tilleston[1] in seven instances. Hydrochloric acid was present or increased in six and diminished in one instance.

Among other factors of etiologic significance concerned in the production of ulcer to which attention has been directed by various authorities are local diseases of the bloodvessels (varicosities) of the esophagus (Abram,[28] Demel[29]) nervous disturbances in the form of cardiospasm (Meulengracht,[18] Schmidt[30]); and trauma (Kraus,[31] Ortmann[32]). It is important to note on the other hand, that Guisez[26] is convinced that many of the so-called simple ulcers of the esophagus are actually only localized chronic inflammatory processes which finally terminate in stenosis without undergoing definite ulceration and that simple ulceration of the esophagus is rare. The cause of the stricture in these cases is according to this authority an initial spasm. When the spasm becomes sufficiently prolonged and persistent, permanent dilatation with stenosis is produced. This observation has also been confirmed by McKinney.[33] An interesting fact still remains as Fisher[34] has pointed out, which further illustrates the similarity existing between duodenal and esophageal ulcerations, namely, the occurrence of ulcerations of the esophagus following external burns.

Ulcerations have been most frequently observed in adults, the condition being most common between the thirtieth and seventieth years.

The ages of our cases ranged as follows.

Years.	Cases.
20 to 30	1
30 to 40	2
40 to 50	4
50 to 60	3
60 to 70	3
Total	13

According to von Hacker and Lotheissen,[2] in those instances in which the diagnosis has been arrived at by means of esophagoscopy or by the detection of cicatrices of ulcers, the disease is evenly divided between males and females. Perhaps when the ulcers are present in the lower segment of the esophagus the proportion is slightly in favor of males. In our 13 cases there were 6 males and 7 females. In the cases collected by von Hacker and Lotheissen the diagnosis was made in 26 instances on the living subject; in 22 by means of esophagoscopy, once at operation for perforation into the abdomen (Sencert[25]) and on three occasions this affection was accidentally noted while operating in the abdomen (Dressman,[35] von Mikulicz[36]).

There were 13 cases of peptic ulcer of the esophagus in our series.

Case History.—The following history presents the most important features of a typical case. B. B., male, aged twenty-eight years, had been complaining of indigestion for the past eight or nine years, consisting of a pressure feeling in the chest around the heart, pyrosis and shortness of breath. Recently, there had been difficulty in deglutition associated with pain at times, beneath the ensiform cartilage and the lower sternum radiating to the back between the shoulder blades. The difficulty in deglutition was more marked recently and especially following solid food. Regurgitation of food was frequent and at times no nourishment was retained for several days. Gaseous eructations and heartburn were frequent and the patient was greatly constipated. He had been living on a very restricted diet, mainly of liquids, and had lost 10 pounds in weight.

On examination, the chest organs were found normal. The abdomen was slightly distended but there were no enlargements or masses present. There was a distinct tenderness in the epigastrium beneath the ensiform cartilage and over the lower sternum. The test meal showed a total acidity of 32, free HCl 18.

The Roentgen ray report was as follows: "The heart and lungs are normal. The esophagus shows a persistent defect at its lower end just above the cardia on fluoroscopic examination as well as in the plates. The stomach, duodenum, and colon are normal." The esophagoscopic examination reveals a definite ulcer with indurated edges above the cardia corresponding in all respects to the picture obtained by means of the Roentgen rays. The diagnosis of chronic ulcer of the lower third of the esophagus was made.

The chart on page 9 presents the important findings of our 13 cases of peptic ulcer of the esophagus.

Symptoms. In most instances, the disease runs an entirely latent course and symptoms are not produced or they may be of so mild a type that the condition may not even be suspected. The initial signs are not sufficiently characteristic to arrive at a diagnosis and only following a considerable period of time are the actual symptoms manifested. In fact, the ulcer may remain latent until perforation or hemorrhage takes place.

The prominent symptoms of this disease are pain, dysphagia, vomiting, hemorrhage and perforation.

1. *Pain.* Pain is a very constant symptom; it occurred in 84 per cent of our cases. It usually appears in the epigastrium, at the xiphoid cartilage or beneath the sternum and frequently radiates to the back between the shoulder blades or over the thorax. Occasionally, there is a definite painful area in the back in the region of the ninth dorsal vertebra. The pain may be mild or intense or of a burning character and is usually increased by pressure in the upper epigastrium or over the lower sternum. According to Sheehan,[37] pressure over the lower pole of the spleen will produce pain in this disease.

Pain, however, may occur even without swallowing, but is always increased during the act of deglutition, a sign which distinguishes it from gastric ulcer. It is usually intermittent in type with periods of relief between meals. It is ordinarily less severe when swallowing fluids. Inasmuch as the pain is usually intense, the patient becomes fearful of food, restricts his diet and becomes very much undernourished.

2. *Dysphagia.* Difficulty in deglutition is also a very prominent sign of the disease. It occurred in all of our cases. At first it is observed only in taking solids, but later there is even great difficulty with liquids and finally but very small amounts of nourishment can be consumed. The difficulty in swallowing is produced by spasm of the esophagus and in consequence regurgitation of food takes place, nutrition is disturbed and the patient loses flesh and strength.

3. *Vomiting.* Vomiting was observed in 54 per cent of our cases. It is produced at first by spasm, later frequently as the result of actual stricture. Regurgitation of food is far more frequent than actual vomiting with which it is often confused. According to von Hacker and Lotheissen,[2] if large amounts of food are regurgitated it may be concluded that a stenosis has been produced as the result of the ulcer.

4. *Hemorrhage.* According to Tilleston,[1] hemorrhage occurs in 53 per cent of the cases but was present in but 23 per cent of ours. At times but small amounts of red or reddish-brown blood are regurgitated, occasionally larger quantities of dark blood of the coffee-ground variety are vomited resulting from the accumulation of small amounts which have slowly passed into the stomach. In some instances, the blood passes entirely or partly through the bowel,

and is detected as melena. In most instances, according to our experience, even when visible hemorrhage is not observed, occult blood is found in the stools. In consequence of these hemorrhages, anemia and loss of strength is produced and finally great loss of flesh and even cachexia occur. In the patient reported by Zahn,[21] death followed as the result of the onset of pernicious anemia. The source of the hemorrhage is from an erosion of a bloodvessel in the ulcer and should bleeding be excessive death may quickly ensue. It is extremely difficult at times to determine whether the hemorrhage arises from the esophagus or stomach. This difficulty is even increased when one recognizes the fact that an ulcer of the stomach or duodenum and esophagus may coëxist. Curshmann[38] has pointed out that in hemorrhage from a ruptured esophageal vessel, the blood usually pours out without producing nausea and straining, as one usually observes in gastric hemorrhage.

Perforation. Perforation occurs in 14 per cent of cases according to Tilleston[1] and is usually fatal. Its presence is indicated by the signs of the sudden onset of a perforative peritonitis or by sudden pain in the chest with dyspnea and collapse followed by pneumothorax or hydropneumothorax. This complication did not occur in any of our cases.

Diagnosis. There is usually great difficulty in arriving at a diagnosis of peptic ulcer of the esophagus and not uncommonly the diagnosis is not made until a fatal complication, such as hemorrhage or perforation, occurs. In other instances, the diagnosis remains obscure until the later stages when stricture with dilatation of the esophagus manifests itself. In some cases, it may be made with a considerable degree of certainty. Whenever ulceration occurs in the lower esophagus, the peptic form should be suspected and the diagnosis only becomes certain if other varieties can be excluded. In arriving at the diagnosis the symptom of pain associated with dysphagia situated beneath the sternum and radiating between the shoulder blades is of great importance. In addition, there is frequently vomiting or regurgitation of food; at first immediately but later following dilatation some time after the ingestion of food, and then usually in large amounts. Tenderness over the lower portion of the sternum or upper epigastrium and in the back is usually present. Additional evidence in favor of this affection is obtained from the coëxistent history of ulceration of the stomach or duodenum as well as by the detection of a constant blood-discolored area following the passage of a thread according to the Einhorn method and the presence of occult blood in the stools. The employment of bougies as an aid in the diagnosis of this condition is not to be recommended. These instruments are extremely dangerous when used in this affection and are apt to produce hemorrhage or perforation even though passed over a thread anchored in the bowel.

Since the advent of fluoroscopy and esophagoscopy, a more com-

plete investigation of the esophagus has been made possible. The Roentgen ray examination may render considerable aid in diagnosis and should always be undertaken before esophagoscopy is performed. Special attention to the technique must be followed in order to note small lesions which may otherwise be overlooked. The subject is at first fluoroscoped in the anteroposterior, lateral, and oblique positions in order to bring the esophagus and the suspected lesion into view. The usual liquid meal of barium and water or with acacia is administered and the opaque meal is viewed as it descends through the esophagus. Four types of defects may be observed in the esophagus: (1) mucosal erosions; (2) niche or penetrating; (3) spastic defects; (4) perforating.

In mucosal erosions, defects are not as a rule observed in the Roentgen ray examination, but frequently in this type of ulcer spastic phenomena are noted which are suggestive of ulcer when constantly present. A small fleck of barium may be observed in the ulcer area. A definite diagnosis can be made from the symptoms together with the esophagoscopic findings.

The niche or penetrating type of ulcer is the most frequent Roentgen ray finding. The filling defect is quite as much characteristic of ulcer as one notes in gastric ulcer. These ulcers are usually small, the craters shallow, but may also be deep, filling and emptying readily as the meal passes over the lesion. They are best observed when the patient is allowed to swallow the liquid meal slowly, and a small fleck of barium is noted in the ulcer crater, which is usually seen when the esophagus is empty. Occasionally, this form of ulcer may be of large size, resembling a diverticulum. These ulcers are usually single but in several instances in our series two ulcers have been found in various portions of the esophagus. Moreover, in a number of our cases we have noted that the patient complained of distress or pain when the meal passed over the ulcerated area. This sign is not only typical of a benign ulcer but is also frequently observed in early cases of carcinoma. The niche type of defect is pathognomonic of ulcer of the esophagus.

Spastic defects are frequently observed on the films as well as by fluoroscopic examination. Three types of defects are usually noted: (1) simple transient spastic defects causing retardation to the opaque meal; (2) a tapering defect of the esophagus toward the cardia; (3) an indentation, resembling an incisura simulating the spastic phenomena observed in gastric ulcer occurring opposite the ulcer defect. This may be noted especially when the ulcer occurs in the lower third and when there is a patency of the cardioesophageal opening; the spastic defect being constant, and the esophagus usually slightly dilated in this area. Cardioesophageal patency occurred in 10 of our cases examined; the type varied from a slight spasm to a marked constriction.

The perforating type of ulcer occurs as a complication of this

IMPORTANT FINDINGS OF 13 CASES OF PEPTIC ULCER OF THE ESOPHAGUS.

Name.	Sex.	Age.	Duration.	Site.	Dysphagia.	Substernal discomfort.	Pain.	Pyrosis.	Vomiting and regurgitation.	Hemorrhage.	Roentgen ray findings.	Esophagoscopic examination.
1. B. B.	Male	28	8 yrs.	Lower third	+	+	+	+	+	0	Patency of cardioesophageal opening; small defect	Small eroded ulcer above the cardia, with indurated edges.
2. H. G.	Female	47	4 mos.	Middle third	+	+	+	0	0	0	Small filling defect	Ulcer on right wall, not indurated.
3. D. E.	Female	50	3 mos.	Upper third	+	+	+	+	+	0	Obstruction, marked spasm, and irregular defect in upper third, spasm in lower third	Indurated ulcer with narrowing of lumen of esophagus.
4. J. J. M.	Male	65	1 yr.	Lower third	+	+	+	0	0	0	Large circumscribed dilatation 4 cm. in diameter, lower end, patency of opening	Large indurated ulcer with dilatation.
5. W. F. W.	Male	47	1 yr.	Lower third	+	+	+	+	+	+	Patency of cardioesophageal opening, with small defect	Ulcer of moderate size with smooth edges and indurated base.
6. S. S.	Male	35	2 yrs.	Lower third	+	+	+	0	+	0	Patency, slight dilatation with small defect	Well-defined ulcerated area with indurated edges
7. W. T. S.	Female	68	Many yrs.	Lower third	+	+	+	+	+	0	Patency of cardioesophageal opening, lumen irregular, small defect, slight dilatation	Ulceration medium sized with dilatation above.
8. H. T.	Female	43	2 yrs.	Lower third	+	+	+	+	+	0	Penetrating ulcer 1 cm. in diameter	Not made.
9. R. C.	Female	55	1 yr.	Lower third	+	+	+	0	0	+	Small filling defect	Indurated ulcer, mucous membrane extremely red and thickened, large bleeding.
10. T. S.	Female	56	4 yrs.	Lower third	+	+	0	0	0	0	Patency of cardioesophageal opening, dilated lumen, irregular, shows a constriction	Large indurated ulcer, thickened mucous membrane.
11. M. B.	Male	42	1 yr.	Upper third	+	+	+	0	0	0	Small defect 5 mm. in diameter, middle third	Small ulcer, edges smooth and not indurated.
12. A. C. C.	Male	31	10 dys.	Upper third	+	+	0	0	0	0	Small defect 3 mm. in diameter	Ulcer ½ cm. in diameter, edges and base indurated, mucous membrane very red.
13. M. L.	Female	60	Many yrs.	Upper and lower third	+	+	+	+	+	+	Two penetrating ulcer defects, one in upper and one in lower third	Not made.

affection, but is rarely observed by the Roentgen ray inasmuch as the patient is ordinarily so extremely ill, that this method of examination cannot be undertaken. This type of ulcer will be fully described in a later experimental communication.

The fluoroscopic examination is the method of choice to be undertaken in the study of the esophagus, as the subject may be placed in the various positions for a study of the esophageal outline. Films, however, are always taken in at least two positions to confirm the fluoroscopic findings. It is also occasionally necessary to have the patient in the recumbent posture drink the opaque meal through a straw in order to observe the esophagus properly filled, but as a rule in ulcer it is usually best to take the films both when filled and empty, as a small amount of barium will frequently remain in the ulcer crater sufficiently long to be demonstrated on the films.

Stricture, as a complication of this condition, occasionally occurs and gives similar Roentgen signs as strictures due to other causes, such as lye or acid burns. In this condition, the esophagus shows obstructive signs with marked dilatation, which must be differentiated from cardiospasm. Marked dilatation was noted in one instance, while small localized circumscribed dilatations were observed in 3 instances. Obstruction was noted in 1 case and slight retardation of the opaque meal observed in 6 instances. Inflammatory masses with induration were observed in 2 instances.

Defects were observed in all of our cases of ulcer of the esophagus, the lower third being the most frequent site. In 2 instances two ulcers were noted, one in the upper and one in the lower end, and in 1 of the cases a gastric ulcer was also observed. In another instance duodenal ulcer was associated with the esophageal ulcer.

The use of the esophagoscope has been of the greatest service in the diagnosis of peptic ulcer of the esophagus and considerable advance in the clinical study of the disease has been accomplished by means of this instrument. Its employment, however, is not a harmless procedure and must be practised with great caution.

Inasmuch as the tube should be introduced while its passage is being visualized, it may be applied under skillful hands with a minimal degree of risk. The ulcer may be observed without the tube actually reaching it and direct information may be observed concerning its presence which cannot be obtained by any other method. In doubtful cases biopsy of the wall will definitely clear up the diagnosis, though this procedure is extremely dangerous. Ulcerations may be mistaken for cancer as occurred in the cases reported by Starck[39] and Tapia[40] in which this error was made while the further course of this affection finally cleared up the diagnosis.

During the past few years, the diagnosis of peptic ulcer of the esophagus has been definitely determined by means of this instrument in many instances. Von Hacker and Lotheissen,[2] in 1920, collected 22 cases in 14 of which the ulcerations were directly

visualized and in 8 the scars of the ulcers, but there are now undoubtedly many more which have not been recorded. Under direct visualization the ulcer lies usually lengthwise and presents a definite loss of substance. The ulcers are usually small, covered with a grayish exudate which bleeds readily; occasionally, especially when the ulcer is situated at the cardioesophageal opening, the ulceration may be very large. The edges are somewhat thickened, sharply defined, showing a definite crater, the base of which is filled with granulation tissue. The surrounding area is frequently indurated and thickened as a result of the chronic inflammatory lesion. At times a bleeding ulcer will be observed, but this finding is more frequently found in the early and acute type. The ulcer bleeds readily when touched by the applicator, which also produces extreme pain in this region. The lumen is not as a rule narrowed, excepting in old chronic untreated cases of long standing in which stenosis with stricture may be found. Spasm of the esophagus is not usually observed in the esophagoscopic examination. Strictures of the esophagus secondary to simple peptic ulcerations are, however, rare but are commonly found in cases resulting from burns due to lye or concentrated acids. These ulcers may, however, resemble chronic peptic ulcers, excepting that they produce large scars and usually cause strictures. Uncomplicated peptic ulcers heal readily under proper treatment and usually show no extensive scar formation. When stricture is observed, the esophagus becomes more markedly dilated, on account of a long-standing obstruction.

Induration and thickening of the esophageal wall may be observed in benign as well as in malignant conditions, and at times it is extremely difficult to determine the exact nature of the lesion.

Fixation of the esophageal wall is an infrequent finding in chronic ulcerations but occurs most frequently in malignant ulceration. This condition occurred in 2 instances in our series, in 1 confirmed by biopsy.

Differential Diagnosis. Peptic ulcers of the esophagus must be differentiated from similar ulcerations occurring in the stomach and duodenum as well as from ulcers in the esophagus due to other causes.

This form of ulceration is distinguished from ulcer of the stomach and duodenum in that the pain appears immediately upon swallowing food and is associated with difficulty in deglutition, while in gastric and duodenal ulcer this symptom appears late, and is not associated with dysphagia. The hemorrhages accompanying ulcer of the esophagus occur suddenly and are violent, occurring without nausea or straining, while in ulcer of the stomach and duodenum there is usually considerable nausea and straining. Tenderness over the sternum is characteristic of esophageal ulceration, epigastric tenderness is more common in the gastric and duodenal disease.

In the differential diagnosis between peptic ulcer of the esophagus from ulcerations due to other causes, there is ordinarily but slight

difficulty. The history of the occurrence of trauma or the history of a preceding infectious disease is usually sufficient to quickly distinguish these affections.

Rupture of varicose veins of the esophagus with consequent hemorrhage may at times cause confusion. Pain and dysphagia are, however, absent in these cases and the usual associated signs of cirrhosis of the liver will ordinarily clear up the diagnosis.

Luetic ulceration can usually be ruled out by means of the Wassermann test, and the tuberculous and the carcinomatous forms by means of the Roentgen ray and esophagoscopy with the addition, if necessary, of biopsy. When stenosis occurs followed by a greater or less degree of dilatation of the esophagus without the previous characteristic history of peptic ulceration, it may become difficult to distinguish this form of stenosis from other varieties. Stenosis following ulcerations due to corrosive poisons or due to foreign bodies can usually be determined by the history; diffuse dilatation due to cardiospasm by means of the Roentgen ray and esophagoscopy. Carcinomatous stricture is determined by its brief history together with the usual signs of carcinoma in addition to the Roentgen ray and esophagoscopic study and, if necessary, biopsy findings.

Course and Duration. While the course of the disease is frequently rapid, it may progress slowly with periods of remission and, as a result of the healing of the ulcer, stricture may occur. The onset, however, is usually gradual, beginning with dyspepsia and finally with pain and dysphagia. In other instances, the ulcer remains latent until hemorrhage or perforation occurs. The duration of the disease is uncertain, varying from a few days to many years. In 63 per cent of Tilleston's cases it was under six months. The duration in our cases ranged between ten days and eight years. There can be but little question that clinical cure is often obtained; however, if death is not caused by perforation or hemorrhage incomplete healing may take place with the formation of esophageal stricture and dilatation. Death is usually due to perforation or hemorrhage but may be caused from inanition or from intercurrent diseases.

Treatment. Inasmuch as focal infections are known to play an important rôle in the etiology of peptic ulcerations all foci of infection should, as far as possible, be eradicated.

The treatment of uncomplicated peptic ulceration of the esophagus is mainly dietetic. An attempt should be made as far as possible to prevent further irritation and maintain rest. Milk as the special form of diet plays a most important rôle. It should be allowed exclusively for a week or ten days and in the very serious forms even as long as two or three weeks. It should be permitted only in small amounts given at frequent intervals. Following this, soft food may be allowed; always, however, in small quantities. Early in the course of the treatment olive oil may be administered. Alkalies should also be prescribed in the form of calcium carbonate,

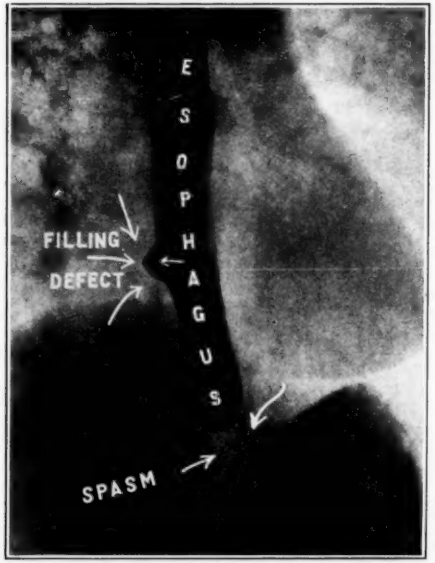

FIG. 1.—Illustrates a typical penetrating ulcer in the lower third of esophagus, on right posterolateral wall. The cardiac end shows definite spasm.

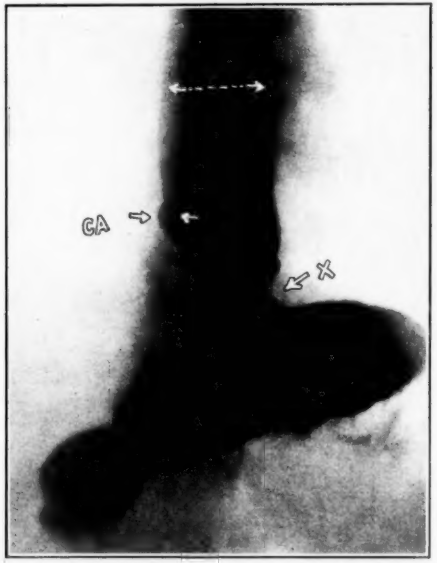

FIG. 2.—A dilated esophagus with obstruction due to carcinoma at the cardiac end involving the cardiac of the stomach. The right posterolateral wall above the obstructed area presents an ulcer defect which is carcinomatous.

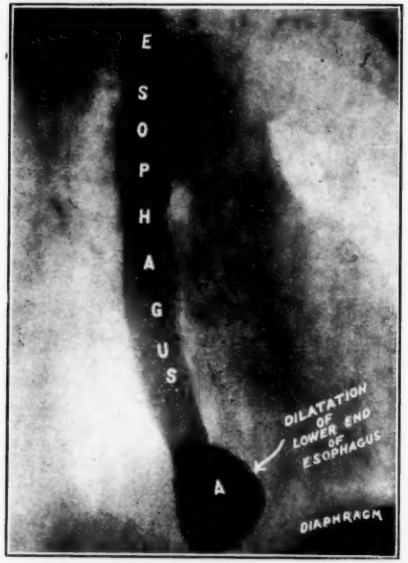

FIG. 3*a*.—Presents a large circumscribed dilatation at cardiac end, due to a chronic ulceration. (Oblique view.)

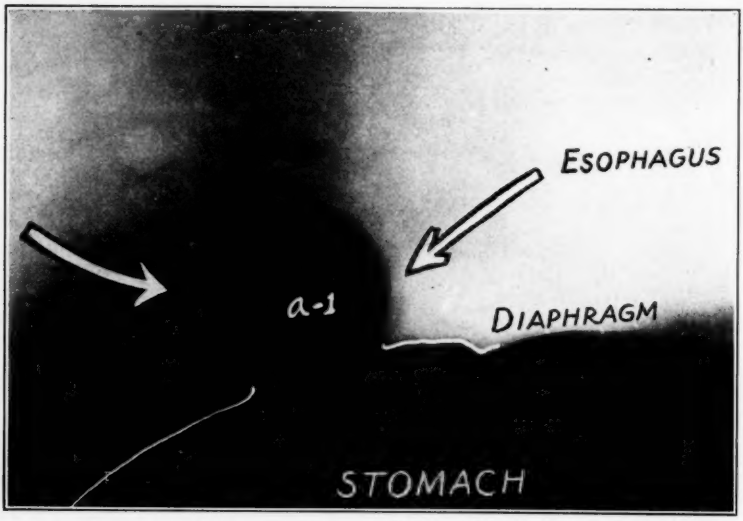

FIG. 3*b*.—Illustrates the same ulcer resembling a diverticulum or hernia of the cardia of the stomach through the esophageal opening. (Anterior view.)

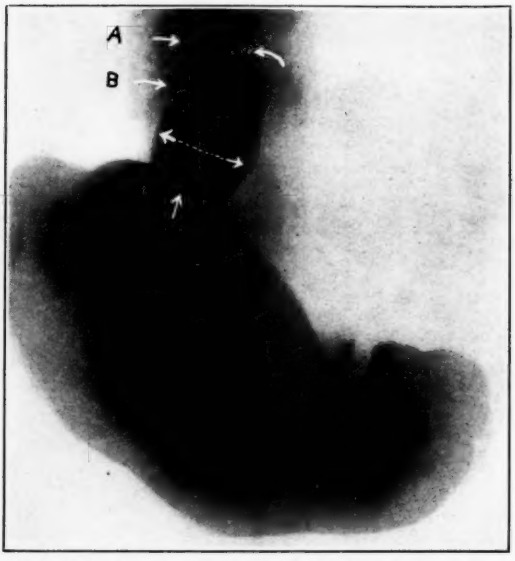

FIG. 4.—A slight dilatation in the lower third of esophagus with a constriction at *A*, and a small indentation on right lateral wall at *B*, the result of chronic ulceration.

sodium bicarbonate and bismuth subcarbonate. The last, especially in large doses, given at bedtime. Belladonna at times gives great relief, especially when spasm is present. In addition to the dietetic treatment in ulcerations of severe type, considerable relief may be afforded by direct application of various remedies through the esophagoscope. Relief from pain may be obtained at times by anesthetizing the ulcer with novocain or it may become advisable to cauterize the area with a solution of zinc chlorid, tincture of iodin or a solution of nitrate of silver, as has been recommended by Abram,[28] von Mikulicz[36] and others. Weiss[41] and Sheehan[37] advise the introduction of the duodenal tube through the esophagoscope, which is to be retained for a period of from three to ten days and is to be utilized as a means of introducing nourishment. During the course of active treatment complete bedrest should be maintained.

If healing does not occur following the treatment already outlined gastrostomy should be performed. The esophagus can thus be placed at rest and nutrition may be fully maintained until complete healing has taken place. This operation was performed with success in the cases reported by Ewald,[42] Tapia,[40] Dressman[35] and others.

Evidence of complete recovery is obtained by the disappearance of symptoms, absence of occult blood in the stools and if deemed advisable by means of a further esophagoscopic and Roentgen ray study. An absence of blood on the Einhorn string test will also afford additional evidence in this regard.

Of the 13 cases in our series, satisfactory relief was obtained in 8 instances by means of the simple dietetic and medical treatment outlined above. In 3 cases the local application of a 10 per cent solution of nitrate of silver in addition accomplished the desired result. One case remained unimproved and 1 died of perforation followed by pneumonia.

Conclusions. Although peptic ulcers of the esophagus are rare, they occur sufficiently often to be of clinical interest. They are usually observed in the lower third of the esophagus though occasionally they are located higher. These ulcers vary greatly in size and are usually single; the right posterolateral wall being most frequently involved. They resemble in many respects ulcers of the stomach and duodenum. Perforations are not uncommon. In large ulcerations, contraction takes place with the formation of stenosis and dilatation. In the small superficial ulcerations, healing is usual and the esophageal lesion is apt to be overlooked. The etiology of peptic ulcer of the esophagus is in every respect similar to that of the stomach and duodenum. In order that this affection may occur, it is necessary that the cardia remain patent so that the regurgitated acid gastric secretion may continue its corrosive effect upon the diseased area in the mucous membrane of the esophagus.

Ulcerations of the esophagus have been most frequently observed

in adults more commonly between the thirtieth and seventieth years and are found equally divided between males and females.

The most prominent symptoms of the disease are pain, dysphagia, vomiting, hemorrhage and perforation. There is often great difficulty in arriving at a diagnosis; however, this may be greatly aided by means of fluoroscopy and esophagoscopy. The treatment consists in the eradication of foci of infection, rest, the regulation of the diet and the administration of olive oil, alkalies and belladonna and at times by the direct application to the diseased area of various remedies such as a solution of nitrate of silver through the esophagoscope. If healing does not occur following this plan of treatment, gastrostomy should be performed to insure adequate feeding and the esophagus kept at rest for a considerable period of time.

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A STATISTICAL STUDY OF CLINICAL AND LABORATORY FINDINGS IN GASTRIC AND DUODENAL ULCER, WITH SPECIAL REFERENCE TO ROENTGENOLOGIC DATA.

Based on the Records of 279 Operatively Demonstrated Cases.

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Introduction. Gastric or duodenal ulcer has been demonstrated at operation in the hospital of the University of Pennsylvania during the past ten years on 279 patients. Many other individuals, diagnosed as having ulcer but not subjected to surgery, have been studied in the medical wards and the roentgenologic department. The present study was initiated with the idea of summarizing and correlating the important data on all the operatively proved cases, but as the work progressed it became apparent that some of the desired information was lacking in many of the records, and that, since under such circumstances each collection of statistical material would represent a different group of patients, it would be impossible to compare accurately the histories, the gastric analyses, the roentgenologic data and the operative findings. In consequence, it was decided to use the entire series only for certain special groups of data, such as the sex and age incidence and the duration of symptoms, and to select for the particular study of symptoms, signs and laboratory data only those cases on which the clinical records were very complete and on which the operative notes were reasonably satisfactory; this latter group includes 36 gastric and 100 duodenal cases. Though the number may be considered too small to have great statistical value, much is gained by the thoroughness with which each case has been studied and the accuracy with which the various groups of data may be compared.

Relative Incidence. The assembled data are presented in the accompanying tables and charts which are largely self-explanatory. Table I shows that the duodenal ulcer cases far outnumber the gastric ones (221 to 58) in the ratio of almost 4 to 1. This relationship is approximately that of the larger surgical clinics. In Moynihan's[1] series of 695 operated ulcer cases, reported in 1923, 531 were duodenal. Until recent years, textbooks stated that gastric ulcers outnumbered duodenal ones, but now almost all statistics quoted indicate the reverse condition and explain the error of former

compilations as due to faulty clinical diagnoses and to a failure of pathologists to examine carefully the duodenum for ulcers and scars. A recent publication by Sturtevant and Shapiro,[2] however, shows that in 7700 autopsies performed at the Bellevue Hospital between 1904 and 1922 more healed and unhealed gastric than duodenal ulcers (120 to 44) were found. The discrepancy between the necropsy and the operative data would seem to be due to the fact that a smaller number of the gastric lesions give rise to symptoms requiring surgical treatment. It is probable, indeed, that many of the gastric cases present no symptoms whatever, since in an analysis of the roentgenologic records, which more nearly represent the total number of patients with ulcer symptoms, Sutherland[3] of the Mayo Clinic found an even greater preponderance of duodenal lesions (9 to 1).

TABLE I.—SEX OF ULCER CASES.

	Gastric.		Duodenal.		Two groups.	
Sex.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Male .	52	90	188	85	240	86
Female	6	10	33	15	39	14
Total .	58	100	221	100	279	100

Sex Incidence. In the sex distribution, which is presented in the same table, it will be noted that 90 per cent of the gastric ulcers and 85 per cent of the duodenal ulcers occurred in men. The preponderance of duodenal ulcer in the male is well recognized, but it is commonly stated that gastric ulcer is more common in women. Although Moynihan,[1] in 164 gastric cases, had an equal distribution between the sexes, Balfour, in 1927, on the basis of the Mayo statistics stated that the sex incidence for the chronic cases was the same as for duodenal ulcer, about 4 to 1 in favor of males. Sturtevant and Shapiro in their autopsied cases found the ratio of men to women about 3 to 1 in each group. While the difficulty in diagnosis renders a decision as to sex distribution in the simple acute erosions or ulcers uncertain, the recent literature and our results suggest that of those coming to operation and seen at autopsy the great majority, both gastric and duodenal, is in the male sex.

Age Incidence. The age incidence for each ulcer group is presented in Tables II to V, which show, for the total series of 279 cases, not only the age at which they were referred to the hospital for study and treatment, but also that at which according to their histories ulcer symptoms first occurred. The actual figures and the percentages are given for the sexes separately and combined.

Three-fourths of the gastric cases (76 per cent) (Table II) were forty or more years of age at the time of admission, the majority of these (57 per cent or 43 per cent of the total number) being in the fifth decade of life; whereas only a half (52.9 per cent) of the duodenal cases (Table III) were aged forty years or over, and the numbers in the fourth and fifth decades were approximately the same (31.7 and

29.8 per cent). Furthermore, three-fourths of the gastric cases (Table IV) had their first digestive symptoms after the thirtieth year and more than 60 per cent of the duodenal cases (Table V). (See Chart I.)

TABLE II.—AGE INCIDENCE IN 58 GASTRIC ULCER CASES AT THE TIME OF ADMISSION TO HOSPITAL, BY SEX AND FOR THE TOTAL GROUP.

	Male.		Female.		Total group.	
Decade.	No.	Per cent.	No.	Per cent.	No.	Per cent.
10 to 19	1	2	..	...	1	2
20 to 29	5	10	..	...	5	8
30 to 39	8	15	..	...	8	14
40 to 49	21	40	4	66	25	43
50 to 59	10	19	1	17	11	19
60 to 69	7	14	1	17	8	14
Total	52	100	6	100	58	100

TABLE III.—AGE INCIDENCE IN 221 DUODENAL ULCER CASES AT THE TIME OF ADMISSION TO HOSPITAL, BY SEX AND FOR THE TOTAL GROUP.

	Male.		Female.		Total group.	
Decade.	No.	Per cent.	No.	Per cent.	No.	Per cent.
10 to 19	1	0.5	..	...	1	0.5
20 to 29	31	16.5	2	6	33	14.9
30 to 39	60	31.8	10	30	70	31.7
40 to 49	57	30.4	9	28	66	29.8
50 to 59	30	16.0	11	33	41	18.5
60 to 69	8	4.3	..	...	8	3.6
70 to 79	1	0.5	1	3	2	1.0
Total	188	100.0	33	100	221	100.0

TABLE IV.—AGE INCIDENCE IN 58 GASTRIC ULCER CASES AT THE TIME OF ONSET OF SYMPTOMS, BY SEX AND FOR THE TOTAL GROUP.

	Male.		Female.		Total group.	
Decade.	No.	Per cent.	No.	Per cent.	No.	Per cent.
10 to 19	2	4	1	17	3	5
20 to 29	11	21	..	...	11	19
30 to 39	13	25	1	17	14	24
40 to 49	13	25	3	49	16	28
50 to 59	9	17	1	17	10	17
60 to 69	4	8	..	...	4	7
Total	52	100	6	100	58	100

TABLE V.—AGE INCIDENCE IN 221 DUODENAL ULCER CASES AT THE TIME OF ONSET OF SYMPTOMS, BY SEX AND FOR THE TOTAL GROUP.

	Male.		Female.		Total group.	
Decade.	No.	Per cent.	No.	Per cent.	No.	Per cent.
10 to 19	12	6.4	2	6	14	6.3
20 to 29	66	35.1	6	18	72	32.6
30 to 39	58	30.8	11	34	69	31.2
40 to 49	31	16.5	10	30	41	18.5
50 to 59	11	5.9	3	9	14	6.3
60 to 69	6	3.2	1	3	7	3.2
?	4	.....	..	...	4	1.9
Total	188	100.0	33	100	221	100.0

Considering next the age distribution according to sex it will be observed, for both the gastric and the duodenal groups, that the men

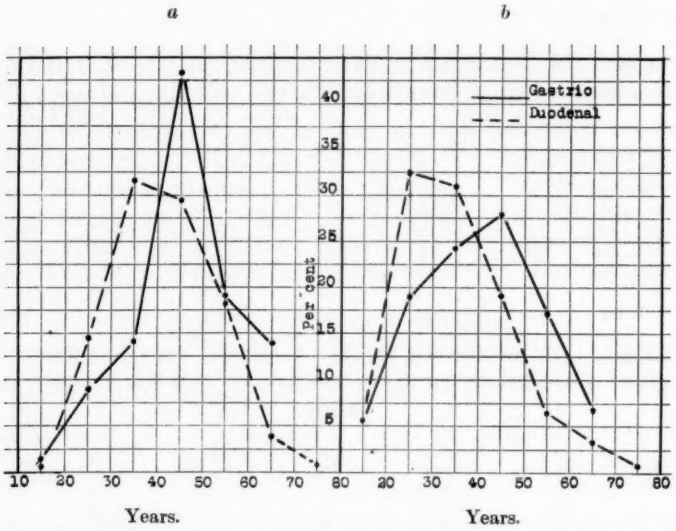

CHART I.—(*a*) Age of gastric and duodenal ulcer cases at time of admission to hospital (58 and 221 cases respectively). (*b*) Age at onset of symptoms in same cases of gastric and duodenal ulcer.

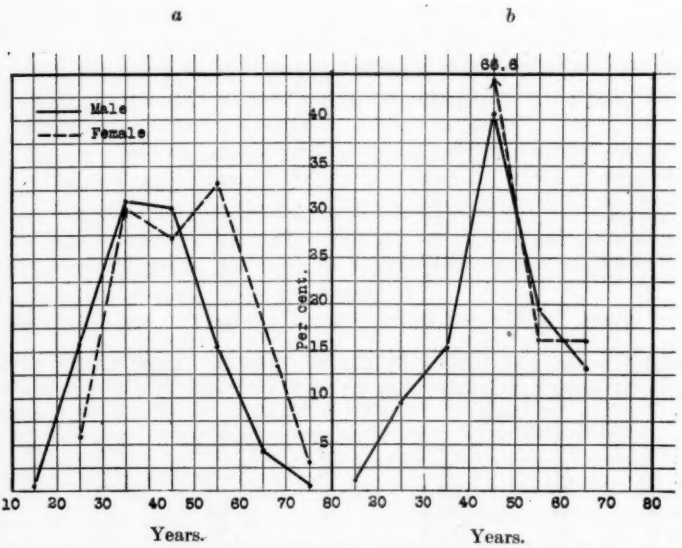

CHART II.—(*a*) Age of male and female duodenal ulcer cases at the time of admission to the hospital (188 and 33 cases respectively). (*b*) Age of male and female gastric ulcer cases at the time of admission to the hospital (52 and 6 cases respectively).

were younger both for the time of hospitalization and for the onset of symptoms. For the admission time, all the women with gastric lesions and 64 per cent of those with duodenal lesions were forty or more years of age against respectively 73 per cent of the men with gastric lesions and 51.2 per cent of those with duodenal lesions. For the time of onset of symptoms, the corresponding figures for the women were 66 per cent gastric and 42 per cent duodenal against 50 and 26 per cent respectively for the men. (See Chart II.)

These results find surprisingly little support in even recent text-books, chiefly because it is still common practice to quote and be guided by statistics compiled years ago on the basis of autopsy findings and of unproved clinical diagnoses. C. F. Martin in Osler's System[4] says that gastric ulcer is most common between twenty and thirty years of age and that the average age for males is 36.7 years and for females 27.1 years. His combined statistics on 704 cases showed 37 per cent in the third decade and 26.5 per cent in the fourth. Speaking specifically of duodenal ulcers he says that they are commonest in the third decade. Aaron,[5] in 1927, speaking of both gastric and duodenal cases, says that in women the period of liability was noted to begin earlier than in men and to reach its maximum at twenty-five to thirty years. Crohn,[6] in the same year, while admitting that ulcer more commonly becomes a clinical problem in the later decades states that its onset can be traced in over half the cases to the period between ten and thirty years of age and that gastric ulcer is more common in younger persons and duodenal ulcer of greater frequency in older individuals. In so doing, he overlooks Gruber's statistics, which he himself quotes, showing 60 per cent of gastric ulcers to occur between forty and seventy years of age. He also gives Fenwick's statement of 1900 to the effect that three-fourths of the cases in females begin before the thirtieth year. Friedenwald,[7] in 1912, in an analysis of 1000 gastric and duodenal cases found the acme of incidence in the third decade, but his cases were not proved. On the other hand, Moynihan,[8] in the same year, analyzing 187 proved duodenal cases found the majority of them in the fourth and fifth decades and Blackford and Dwyer,[9] in a recent paper covering 332 cases found the average age at the time of diagnosis to be forty-one years for duodenal ulcer and forty-eight for gastric ulcer; they found 66 per cent of the former group seeking relief before forty-five years of age and only 33 per cent of the latter.

Symptoms. *Pain.* The outstanding and almost universal symptom of peptic ulcer is upper abdominal pain and in Table VI are given the terms used by our patients to describe the nature of the pain from which they suffered. Not infrequently several adjectives were employed in a single case: each has been recorded, and the totals for the vertical columns are, therefore, greater than the number of cases studied. It is interesting to note that, with the

exceptions of "burning" and "gnawing," the adjectives occurred with almost equal frequency in the two groups. These exceptions, however, would seem to be of significance, since the term "burning" appears five times more often in the gastric series and "gnawing" only in the duodenal group. If burning pain indicates, as Hurst has claimed, acid regurgitation into the esophagus our findings would suggest that this happens much more often in cases of gastric ulcer. Gnawing pain is often attributed to overactive gastric peristalsis and yet only 5 of our 18 duodenal ulcer cases with this type of distress had hyperperistalsis on fluoroscopic examination, and only 8 had a residue of the barium meal after six hours; high acidity of the gastric contents was the condition most frequently associated (14 of the 18 cases). Severe pain occurred in almost one-third of each group and was associated with high gastric acidity in three-fourths of the cases; and with pyloric stenosis and adhesions, each, in one-half.

TABLE VI.—NATURE OF THE PAIN IN ULCER CASES.

Descriptive term used by patient.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases).
	No.	Per cent.	No. and per cent.
Severe	11	31	28
Dull	7	19	28
Sharp	9	25	18
Gnawing	..	..	18
Burning	14	39	8
Cutting	..	..	5
Boring	..	..	4
Aching	1	3	5
Colicky	..	..	4
Sense of fullness	1	3	3

TABLE VII.—LOCATION OF PAIN IN ULCER CASES.

Location.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases).
	No.	Per cent.	No. and per cent.
Epigastrium	28	78	92
Back	7	19	15
Right hypochondrium	4	11	2
Left hypochondrium	3	8	7
Lower abdomen	1	3	3
Left chest	2	6	
Shoulder	..	..	2

The location of the pain (Table VII) was usually, as is generally recognized, in the epigastric region (78 per cent for the gastric series and 92 for the duodenal). Of the 7 gastric ulcer cases having pain in the back, usually associated with epigastric pain, 4 had deeply penetrating lesions, 2 involving the lesser curvature and the other 2 the posterior wall of the stomach near the lesser curvature. Two others had indurated posterior wall ulcers, but the seventh was a gastroduodenal ulcer case without, so far as the records indicate, any involvement of the posterior wall. Of the 15 duodenal cases

with back pain 1 had an adhesion of the ulcer area to the pancreas, 2 had adhesions to the posterior wall of the abdomen, 2 others had gastric adhesions, a sixth one presented fibrous connection with the gall bladder, and a seventh and an eighth, adhesions about the appendix and duodenum, respectively: others, though specific adhesions were not mentioned, had old indurated ulcers that had existed for from two to ten years. It is quite probable that some of these also had posterior connections. One other case with back pain should be referred to as it was our only instance of ulcer in the second part of the duodenum; another was at the junction of the first and second parts. It would appear, therefore, that when an ulcer patient complains of referred pain in the back the probabilities are that the ulcer is an old one and that there exist adhesions to structures posterior to the stomach. The occasional complaint of right or left upper quadrant pain did not seem to have significance, though of the 2 gastric cases having left chest pain the lesions were high on the lesser curvature and 1 was of the deeply penetrating type.

TABLE VIII.—TIME OF PAIN IN ULCER CASES.

Time in relation to meals.	Gastric ulcer.		Duodenal ulcer.
	No.	Per cent.	No. and per cent.
Immediately after	5	14	2
Within one-half hour after	1	3	1
One-half to one hour after	3	8	8
One to two hours after	9	25	12
Two to three hours after	1	3	29
Three to four hours after	2	6	15
No relation	11	30	13
Not stated	4	11	30
Total	36	100	100

Table VIII shows that in most instances a fixed time relation of the pain to meals existed, but that the interval between the ingestion of food and the onset of the pain varied considerably. In a large way it may be pointed out that the gastric lesions tended to give a shorter interval than the duodenal ones (the largest percentage of those in which a relationship existed having a period of one or two hours against a period of two or three hours for the duodenal cases). It has been stated that the higher the lesion in the stomach the sooner the pain after food, but our data do not lend support to this idea and, furthermore, it is difficult to explain the time variation in the duodenal cases on such a basis. Of those having no food-pain relationship the majority was gastric: this cannot be explained on the basis of gastric retention since a gastric residue six hours after a barium meal occurred with about equal frequency in the two groups.

Various factors give temporary relief from the pain caused by these ulcers but the ingestion of food was the most frequent factor

in our series (36 per cent for the gastric group and 57 per cent for the duodenal group), as showed in Table IX. The administration of alkalies was next most effective in each group. This relief undoubtedly comes as a result of neutralizing the acid gastric contents, but whether such neutralization acts by lessening direct chemical irritation of the ulcer area or by decreasing peristalsis and local spasm is not settled. This is a problem which we plan to investigate by means of simultaneous fluoroscopic observation and chemical studies on gastric and duodenal contents. Vomiting also probably acts as a means of relieving pain by ridding the stomach of the stimulating material.

TABLE IX.—FACTORS PRODUCING RELIEF OF PAIN IN ULCER CASES.

Factor.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases).
	No.	Per cent.	No. and per cent.
Ingestion of food	13	36	57
Administration of alkalies	8	22	44
Vomiting	9	25	23
Pressure	1	3	2
Eructations	3	8	
Catharsis	1	3	2

TABLE X.—FREQUENCY OF PHENOMENA OTHER THAN PAIN IN ULCER CASES.

Phenomenon.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases).
	No.	Per cent.	No. and per cent.
Vomiting	27	75	68
Eructations	21	58	64
Nausea	12	33	35
Hematemesis	15	42	19
Appetite:			
Good	10	28	29
Poor	13	36	11
Not stated	13	36	60
Bowels:			
Constipated	17	47	56
Diarrhea	1	3	6
Normal	10	28	20
Not stated	8	22	18
Periodicity of symptoms	22	61	64

Other Symptomatic Phenomena. All of the phenomena referred to in Table X have some bearing on diagnosis when considered in connection with characteristic pain and other special diagnostic findings, but, with the exception of hematemesis, have far less significance than has pain itself. Vomiting, eructations and nausea are present in so many gastric and even extragastric conditions that their presence alone or combined means little or nothing. Fortunately they occur rarely in ulcer cases without associated pain. Macroscopic blood in the vomitus is of great importance and should always suggest the possibility of ulcer even when there are no other

symptoms. It will be noted that 42 per cent of the gastric cases and 19 per cent of the duodenal ones showed it; this figure for the gastric series would probably be lower in a larger series, since in the Mayo cases for 1921 and 1922 (1072 cases) only about one-fifth of each group showed gross hemorrhage. The appetite was more often impaired in the gastric than in the duodenal cases, for which we have no explanation since retention occurred with equal frequency in the two groups. Our figures support the general opinion that ulcer patients are frequently constipated, but the percentages are not greater perhaps than for hospital cases as a whole. Periodicity of symptoms is of considerable diagnostic importance. By this term is meant the presence of characteristic symptoms over periods of months with intervening periods of months or even years in which no such symptoms are manifest. It will be noted that it occurred in each group, and with about the same degree of frequency.

TABLE XI.—NUMBER AND PERCENTAGE OF ULCER CASES THAT PERFORATED, BY DECADES AND FOR THE TWO GROUPS.

	Gastric cases.			Duodenal cases.		
Decade.	Total No.	No. perforating.	Per cent perforating.	Total No.	No. perforating.	Per cent perforating.
10 to 19	1	1	100	1	1	100
20 to 29	5	3	60	33	5	15
30 to 39	8	2	25	70	8	16
40 to 49	25	3	12	66	7	11
50 to 59	11	2	18	41	6	15
60 to 69	8	0	0	8	4	50
70 to 79	..	..	...	2	0	0
Total	58	11	19	221	31	14

Incidence of Perforation. Perforation occurred in 42 of our series of 279 cases (15 per cent): 11 of the gastric group (19 per cent) and 31 of the duodenal (14 per cent) (Table XI). No special decade of life showed a preponderance of these: 19, 24, 24 and 19 per cent occurring respectively in the third, fourth, fifth and sixth ten-year periods. These figures are in agreement with those of Dunbar[10] who, in a large series of 387 perforating cases, found 21.9, 29.2, 20.6 and 17.2 per cent in the same respective decades. Of the ulcer cases occurring in each decade, the percentage that perforated is showed in the table. It will be noted that each of the 2 cases under twenty years of age perforated, that the next highest percentage for the gastric cases was in the third decade, that the frequency of perforation for the duodenal cases for the third, fourth, fifth and sixth decades was about the same, and that 4 of the 10 cases in the seventh and eighth decades (40 per cent) perforated. Table XII shows that in 2 of our gastric cases and in 5 of the duodenal ones perforation occurred without a preceding history of digestive trouble, but all the others gave such a history, though symptoms had been present in most of the gastric cases less than a year.

TABLE XII.—DURATION OF DIGESTIVE SYMPTOMS IN ULCER CASES THAT PERFORATED (IN TOTAL SERIES OF 279 CASES).

Time.	Gastric. Number.	Duodenal. Number.
None before perforation	2	5
One month or less	2	7
Two to eleven months	4	1
One to two years	..	5
Three to four years	..	6
Five to nine years	..	5
Ten years or more	3	2
Total	11	31

TABLE XIII.—DURATION OF SYMPTOMS BEFORE ADMISSION TO HOSPITAL IN 279 ULCER CASES.

Time.	Gastric.		Duodenal.	
	No.	Per cent.	No.	Per cent.
None before perforation	2	3	5	2
One month or less	5	9	14	6
Two to eleven months	8	14	19	9
One to two years	13	22	36	16
Three to 4 years	5	9	32	15
Five to nine years	12	21	53	24
Ten to fourteen years	6	10	27	12
Fifteen or more years	6	10	31	14
Not stated	1	2	4	2
Total	58	100	221	100

Duration of Symptoms. The duration of symptoms in the total series of 279 ulcer cases (Table XIII) is similar for the two groups, and the variation in the time is striking. The ones showing no preceding digestive symptoms were admitted because of perforation. Approximately a fourth of the gastric and a sixth of the duodenal cases had been troubled for less than a year. More than 10 per cent of each group had had symptoms for fifteen or more years and a few stated that they had always had spells of indigestion.

TABLE XIV.—PHYSICAL FINDINGS IN ULCER CASES.

Positive finding.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases).
	No.	Per cent.	No. and per cent.
Spot of tenderness	21	57	38
Muscular rigidity	5	14	7
Palpable mass	3	8	4
Visible peristalsis	2	6	5
Oral sepsis	21	57	?

Physical Examination. Although Moynihan states that an accurate diagnosis of peptic ulcer may be made without a physical examination, Table XIV shows that 57 per cent of our gastric and 38 per cent of our duodenal cases had a definite spot of epigastric tenderness. Such a finding, together with a suggestive history, is

frequently of diagnostic aid, but it may occur in the absence of ulcer. When, in addition, there is muscular rigidity or a palpable mass or visible gastric peristalsis the physical examination becomes of great importance. In 1 of our cases with a palpable mass an old duodenal ulcer with calcified glands about it was found; another had an old healed ulcer with adhesions producing a diverticulum of the duodenum; others with a mass had no unusual findings at operation but Roentgen ray study showed pylorospasm and this doubtless produced the mass that was felt. Two of the gastric cases with muscular rigidity had deeply penetrating ulcers. The cases with visible peristalsis, with a single exception, had pyloric stenosis or spasm with gastric retention.

TABLE XV.—GASTRIC RETENTION IN ULCER CASES (THOSE HAVING SIMPLE TEST MEAL).

Amount of contents 45 to 60 minutes after test meal.	Gastric ulcer (16 cases).		Duodenal ulcer (47 cases).	
	No.	Per cent.	No.	Per cent.
Less than 100 cc.	6	38	13	28
100 to 200 cc.	5	32	19	40
200 to 300 cc.	2	12	7	15
300 to 400 cc.	1	6	4	9
400 to 500 cc.	1	6	2	4
500 to 600 cc.	1	6	2	4
Total	16	100	47	100

Gastric Analysis. During recent years our patients have been given fractional test meals routinely and in consequence only the earlier ones, whose total gastric contents were removed forty-five minutes to one hour after ingestion of the Ewald meal, could be used in the preparation of Table XV. The amounts obtained at that time have been grouped; and, if we consider, as is usually done, a quantity over 100 cc. as indicative of gastric retention, it will be observed that 62 per cent of the gastric cases showed retention and 72 per cent of the duodenal ones. An almost equal percentage showed, by fluoroscopic examination, a moderate to marked residue of the barium meal after six hours. It is our belief that such a simple total removal of the gastric contents forty-five minutes to one hour after the administration of an Ewald meal is as satisfactory a method of showing the degree, if any, of gastric retention as is the usual roentgenologic study.

Table XVI gives the maximal free hydrochloric acid concentration and total acidity of the gastric contents after Ewald meals in 30 of the gastric and 83 of the duodenal cases. In the others it had not been considered safe to introduce a gastric tube. Forty-six per cent of the gastric cases had free hydrochloric acid figures (20 to 39) that are within so-called normal limits, whereas 41 per cent had what has by some been considered hyperchlorhydria. Only 1 case had no free hydrochloric acid. All the duodenal cases had some free acid, but

in 7 per cent it was below normal; on the average the acidity in these cases was higher than for the gastric group. Rehfuss[12] found the total acidity in excess of 70 in 38 per cent of his series of gastric ulcer cases, but he also found that 40 to 45 per cent of supposedly normal individuals had a concentration higher than that. Bennett and Ryle[13] in a series of 100 healthy men found some free acid concentrations as high as 100 and concluded that a high acid figure cannot in itself be regarded as a pathologic finding. Bell[14] in 24 gastric ulcer cases found the acidity low in 33 per cent, intermediate in 21 and high in 46; in 34 duodenal ulcers he found the respective percentages to be 12, 9 and 79. Moynihan[1] in 39 gastric ulcer cases

TABLE XVI.—FREE HYDROCHLORIC ACID CONCENTRATION AND TOTAL ACIDITY OF GASTRIC CONTENTS IN ULCER CASES (HIGHEST FIGURES WHEN FRACTIONALS DONE).

Amount required to neutralize 100 cc. N/10 NaOH.	Gastric ulcer (30 cases).				Duodenal ulcer (83 cases).			
	Free HCl.		Total acidity.		Free HCl.		Total acidity.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
0	1	3						
10 to 19 cc.	3	10	1	3	6	7		
20 to 29 cc.	7	23	..	...	7	8	1	1
30 to 39 cc.	7	23	1	3	13	16	6	7
40 to 49 cc.	8	27	5	17	14	17	4	5
50 to 59 cc.	1	3	6	21	17	21	6	7
60 to 69 cc.	2	7	7	23	6	7	15	18
70 to 79 cc.	..	...	7	23	12	14	14	17
80 to 89 cc.	1	4	1	4	5	6	8	10
90 to 99 cc.	..	...	2	7	3	4	12	15
100 to 109 cc.	..	...	..	...	..	...	6	7
110 to 119 cc.	..	...	..	...	..	...	6	7
120 to 129 cc.	..	...	..	...	..	...	2	3
150 to 159 cc.	..	...	..	...	..	...	3	3
Total	30	100	30	100	83	100	83	100

found intermediate acidity in 34.2 per cent and high acidity in only 20.9 per cent; whereas in 71 duodenal cases he found 72.7 per cent to have high acidity. Rehfuss in 100 cases of duodenal ulcer got a high acid curve in 78 per cent and Ryle[15] quotes figures which show 70 per cent of chronic duodenal ulcers with high acidity and 30 per cent with intermediate acidity; none with low acidity and achlorhydria. Our data, together with those quoted, would seem to indicate a tendency toward high acidity in both gastric and duodenal ulcer, greater in the latter, and yet gastric ulcer may occur with no free hydrochloric acid and duodenal ulcer only rarely, if ever, has an acid concentration greater than may be found in certain presumably healthy persons.

ROENTGENOLOGIC CONSIDERATIONS.

By Eugene P. Pendergrass, M.D.

Table XVII gives the roentgenologic findings under six headings. The type of stomach has been divided roughly into three classes, the grouping being made with regard to the position of the stomach rather than the tone. A level corresponding to the upper limits of the crests of the ilia has been used arbitrarily as the dividing line. Any stomach that had the greater curvature on the level with the crests of the ilia was regarded as the fish-hook type, above steer horn and below ptotic, the films being made in the erect posture.

TABLE XVII.—ROENTGENOLOGIC FINDINGS IN ULCER CASES.

Roentgenological finding.		Gastric ulcer (36 cases). No.	Gastric ulcer (36 cases). Per cent.	Duodenal ulcer (100 cases). No. and per cent.
Anatomic type of stomach	Fish-hook	15	42	64
	Steer-horn	6	17	14
	Ptotic	13	36	19
	Not stated	2	5	3
Residue of barium meal in stomach after six hours	Slight	3	8	21
	Moderate	6	17	19
	Marked	13	36	17
	Complete	4	11	3
	None	9	25	36
	Not stated	1	3	4
Type of gastric peristalsis	Hyperperistalsis	21	59	65
	Hypoperistalsis	8	22	15
	Normal	5	14	15
	Not stated	2	5	3
Degree of gastric motility	Hypermotility	20	55	51
	Hypomotility	14	39	26
	None	..	..	5
	Normal	1	3	15
	Not stated	1	3	3
Pyloric spasm	Present	17	48	30
	Absent	8	22	53
	Uncertain	3	8	6
	Not stated	8	22	11
Constant defect in films	Present	31	86	92
	Absent	5	14	6
	Not stated	..	..	2

The table shows that both the gastric and the duodenal ulcers occurred most frequently in the fish hook, or prevailing type of stomach, the second in frequency being in the ptotic variety. This data is probably of no significance except in correcting an impression of ours; that the ulcers would probably be found most frequently in the ptotic variety of stomach because of the mechanical factor of decreased motility with subsequent decreased tonicity. The position of the stomach is probably of no significance, therefore, if one is justified in drawing conclusions on such a small series of cases.

The amount of residue as indicated in the table is self-explanatory.

It will be noted that a residue occurred in 26 (72 per cent) of the gastric cases and 60 (60 per cent) of the duodenal group. The causes of residue in the gastric cases were as follows: 15 gave evidence of pylorospasm, 4 had organic obstruction, and in 7 we found no specific explanation.

Of the duodenal cases (60) showing retention after six hours, 23 showed pylorospasm and 20 organic obstruction; no explanation can be given for the residue in the other 17 cases. Our finding of 60 per cent with gastric residue is greatly in excess of that reported by Carman[16] who in larger series of 417 duodenal ulcer cases observed that a residue occurred in 25 per cent. If, however, the 11 cases of pyloric stenosis and the 9 cases of gastroduodenal ulcer are excluded, the percentage showing retention is reduced to 40, and this approximates the figures given by other observers.

The type of gastric peristalsis, whether normal, excessive or subnormal, has been based on the activity of the stomach as disclosed after a ten to fifteen minute fluoroscopic examination. No attempt is made to further subdivide these groups, although every roentgenologist recognizes at least various subtypes of hyperperistalsis and we have observed them. Fifty-nine per cent of the gastric and 65 per cent of the duodenal cases showed some form of excessive peristalsis. In the group of gastric ulcers, the waves were either interrupted at the site of the ulcer or they began below it. Continuous waves of hyperperistalsis were more often noted in the gastric group and paroxysmal waves of hyperperistalsis with intermittent periods of inactivity were more frequently observed in the duodenal ulcer series. Antiperistalsis was noted in a few cases of extreme pylorospasm and stenosis. Hypoperistalsis was noted in stomachs that had very little tone in both groups; in the duodenal group it occurred more often in the lesions with which there was an associated marked residue. Not infrequently these lesions had been present for a long time, possibly accounting, therefore, for the lack of tone.

By gastric motility is meant the passage of stomach contents into the duodenum and the term has no reference to peristaltic activity. Hypermotility was observed in 20 (55 per cent) gastric, and 51 (51 per cent) duodenal cases. The former figure is surprising since it is generally assumed that hypermotility does not occur in the presence of pylorospasm. In our gastric cases 48 per cent had pylorospasm, as against 30 per cent in the duodenal group. More careful analysis reveals, however, that of the 20 gastric cases 6 had definite pyloric spasm at some time during the fluoroscopic examination. It must be admitted, therefore, that hypermotility, as we interpret it, can occur when spasm of the pylorus is present. In the 6 cases with pylorospasm and hypermotility 4 ulcers were located on the lesser curvature and 1 was on the greater curvature but 1 was a small ulcer near the pylorus. The relatively low percentage (51) of hypermotility in the duodenal group is to be explained by the fact

that we included 20 cases with organic pyloric obstruction. Exclusive of these and of those in which no statement of motility is made, hypermotility occurred in 66 per cent and normal motility in 20 per cent. In the 14 gastric cases having hypomotility, 10 had pyloric spasm, 3 had organic stenosis at operation and the other a large sclerosing ulcer near the cardia.

Pyloric spasm, presumably a reflex phenomenon from gastric ulceration, was present in only 17 (48 per cent) of our gastric cases. This figure is less than anticipated, and occurred most often when the lesion was near the pylorus (13 of the 17 cases); in 3 cases the ulcer was on the lesser curvature and in 1 on the greater. When definitely stated that no spasm was present, the lesion was high on the lesser curvature except in two instances in which the gastric ulcer reached the pyloric ring (gastroduodenal ulcers). If the cases in which no statement of spasm was made, and in which it was uncertain, are excluded, pylorospasm occurred in 68 per cent of the gastric series. Calculating in the same way 36 per cent of the duodenal cases showed pylorospasm and in these the ulcer was found just distal to or at least very near the pyloric ring.

A great deal of diagnostic importance has been placed on the presence or absence of a constant filling defect in the films of the above series of cases. Only 11 cases, 5 gastric (14 per cent) and 6 (6 per cent) duodenal out of the entire series failed to show such a defect. Pancoast[17] has always laid a great deal of stress upon a routine which consists of a fluoroscopic and a roentgenographic study. For instance, a deformity of the stomach or duodenum appearing in the films may be due to a number of lesions, and without a fluoroscopic examination one hesitates to make a differential diagnosis. Likewise, fairly typical fluoroscopic phenomena cannot be regarded as entirely diagnostic without a filling defect. It is true that one not infrequently ventures the opinion of a nondeforming ulcer, yet such a diagnosis cannot be accepted as readily as if there were a small defect present. The filling defect itself may be and usually is due to a small lesion plus spasm or adhesions, except when there is definite cicatrization present.

The roentgenologic diagnoses and the operative findings in the 36 gastric ulcer cases are presented in Table XVIII. It is felt that with the exception of the 2, in which the stomach was said to be negative, these diagnoses may be accepted as correct (94 per cent). Both of the errors occurred in the patients who had very small ulcers on the lesser curvature and in 1 of these, because of extreme anemia following a gastric hemorrhage, the examination had not been complete. It is at times impossible for the roentgenologist to state with certainty whether a gastric deformity is due to ulcer or adhesions, but usually his demonstration of the filling defect alone is sufficient, when the clinical history is taken into consideration, to establish the exact diagnosis. This is our justification for including

as correct the 4 cases reported as ulcer or adhesions. The definite determination of pyloric stenosis is considered a diagnosis in itself, justifying operation no matter what its cause, and the roentgenologist cannot be expected, in the usual case, to go further.

TABLE XVIII.—ROENTGENOLOGIC DIAGNOSES IN 36 PROVED GASTRIC ULCER CASES.

Diagnosis.	No.	Operative findings.
Ulcer of the lesser curvature	19	Seventeen on lesser curvature, 2 on posterior wall near pylorus.
Gastric ulcer, location not stated	4	One on posterior wall, 1 on lesser curvature, 1 on greater curvature, location of other not stated.
Gastric ulcer or adhesions	4	One on lesser curvature, 1 near pylorus, location of others not stated.
Pyloric obstruction	3	All showed stenosis associated with gastric ulcer.
Gastric ulcer or subtotal gastrectomy	1	Large ulcer on lesser curvature near pylorus with adhesions.
Gastric ulcer, probably on posterior wall	1	On posterior wall near greater curvature.
Gastric ulcer at pylorus with crater	1	Confirmed.
Gastric ulcer or carcinoma	1	On lesser curvature.
Stomach negative	2	Both showed ulcer on lesser curvature, one being very small.

Diagnosis correct in 94 per cent of cases.

TABLE XIX.—ROENTGENOLOGIC DIAGNOSES IN 100 PROVED DUODENAL ULCER CASES.

Diagnosis.	Number and per cent.	Special operative findings.
Duodenal ulcer	15	Confirmed.
Duodenal ulcer probably	13	All ulcers.
Duodenal ulcer or adhesions	29	All ulcers.
Duodenal ulcer and adhesions	7	Confirmed.
Duodenal adhesions	3	One healed, 1 very small ulcer, 1 ulcer and adhesions.
Duodenal adhesions probably	6	Three healed, 1 at junction first and second portions, 1 small on anterior wall, 1 large on posterior wall.
Duodenum uncertain because it was not shown on films	2	One large stellate, first portion; 1 small, indurated, near pylorus.
Duodenum negative	1	Ulcer of second part of duodenum.
Pyloric ulcer	4	Two were pyloric; 2 duodenal.
Pyloric stenosis	11	Two ulcers at pylorus, 9 beyond it.
Gastroduodenal ulcer	9	One was typically pyloric; 8 on duodenal side.
Total	100	
Diagnosis practically correct	88	
Diagnosis missed	12	

In the duodenal group analyzed in Table XIX there are several diagnoses that should be discussed. Three cases were diagnosed duodenal adhesions and 6 probable duodenal adhesions. In these 9 cases, the films showed an inconstant filling defect, and there was an absence of fluoroscopic phenomena that would suggest an ulcer.

It is rather interesting to note that 4 of these cases had healed ulcers. Possibly one should make a diagnosis of ulcer or adhesions with the majority of evidence in favor of one or the other. This seems logical when we appreciate that the major portion of a given filling defect may be spasm or spasm plus adhesions.

In the group "duodenum uncertain because it was not shown on films" the fluoroscopic phenomena were not typical and the examination should have been repeated, but the clinical phenomena were suggestive enough to justify operation without additional confirmatory evidence.

One case was diagnosed "duodenum negative," and at operation an ulcer was found in the second portion of the duodenum. Fortunately, ulcers occur in the second portion very rarely,[16] and when they do one can occasionally make the diagnosis by the fluoroscopic phenomena. Direct evidence of the ulcer cannot be obtained in the second portion because of the rapid motility. The duodenal bulb is the only part in which there is a normal stasis.[16]

TABLE XX.—MORE COMPLETE ROENTGENOLOGIC DIAGNOSIS AND OPERATIVE FINDINGS IN 11 PROVED DUODENAL ULCER CASES LISTED UNDER HEADING OF PYLORIC STENOSIS IN TABLE.

No. of case.	Roentgenologic diagnosis.	Operative findings.
19	Pyloric stenosis, with 18 hour retention. No filling of duodenal cap.	Old crater-like ulcer with annular contraction 1 inch beyond pylorus.
33	Pyloric obstruction. Ulcer or secondary carcinoma of stomach (?)	Large callous ulcer 1 inch beyond pylorus.
41	Pyloric stenosis due to ulcer or carcinoma.	Duodenal ulcer producing complete obstruction.
63	Pyloric obstruction with spasm. Duodenum uncertain due to lack of filling.	Ulcer of first part of duodenum with adhesions.
66	Pyloric obstruction with dilatation; cause uncertain; 48-hour retention.	Dilated and atonic stomach. Ulcer on anterior wall of duodenum near pylorus.
70	Pyloric obstruction with gastric dilatation. Duodenum probably negative.	Ulcer of first part of duodenum.
75	Pyloric obstruction with spasm. No visible ulcer. Duodenum uncertain due to lack of filling.	Small ulcer at pylorus.
93	Pyloric obstruction.	Large indurated ulcer ½ inch beyond pylorus.
106	Pyloric obstruction: carcinoma, ulcer or adhesions.	Old indurated ulcer of duodenum.
125	Pyloric stenosis. No filling defect due to stenosis.	Callous duodenal ulcer.
143	Pyloric stenosis. Pyloric ulcer. Duodenum uncertain.	Ulcer of pylorus.

The diagnosis of "pyloric stenosis and gastroduodenal ulcer" was made on 20 occasions in this group and of these 17 cases had the pathology on the duodenal side. The gastroduodenal ulcer is

possibly an earlier stage of pyloric stenosis when one gets enough filling of the duodenal bulb to show the defect and its extension to the pylorus. This ulcer may ultimately cause obstruction from either cicatrization, spasm, or both. Pyloric obstruction is essentially an entity and will always remain so and the patient is operated upon to relieve the obstruction.

To summarize the findings in Table XIX one will note that the diagnosis was essentially correct in 88 instances, and missed in 12. Of the 12 cases, 4 had healed ulcers, 2 definitely active ulcers and 2 in which the duodenum was not shown, and finally there was 1 case in which there was no filling defect in the duodenal bulb but an ulcer was found in the second portion.

Table XX referring to the 11 pyloric stenosis cases does not need any further comment.

Summary and Conclusions. The clinical and laboratory data on 279 operatively proved gastric and duodenal ulcer cases, representing a ten-years' experience in this hospital, are analyzed, especial attention being given to a selected group of 36 gastric and 100 duodenal cases. The duodenal outnumbered the gastric cases in the ratio of 4 to 1, and it is pointed out that for all of those presenting symptoms the duodenal preponderance is even greater. The male sex predominated in each group (85 to 90 per cent) and the women were on the average a little older than the men. Aside from the roentgenologic findings, the history was of greatest diagnostic importance and sometimes afforded evidence suggesting the gastric or duodenal localization of the lesion. The physical examination was of less diagnostic importance, although the finding of a small spot of epigastric tenderness occurred in almost one-half of the cases and was regarded as of confirmatory value. Both groups of cases showed a tendency to high gastric acidity, more marked in the duodenal, but it is emphasized that such high acidity may occur in individuals free of all evidence of disease and so in itself cannot be accepted as evidence of ulcer.

The roentgenologic findings may be summarized as follows:

1. The roentgenologic diagnosis was correct in 94 per cent of the gastric and 88 per cent of the duodenal ulcers.

2. The most important roentgenologic diagnostic sign was the filling defect.

3. In 23 cases, that were diagnosed either pyloric stenosis, gastroduodenal ulcer or pyloric obstruction only six ulcers seemed to be pyloric in origin, the others being distinctly duodenal.

4. Healed ulcers give similar filling defects to adhesions or ulcer, but do not have associated suggestive fluoroscopic phenomena.

Our thanks are due Dr. G. P. Muller and Dr. E. L. Eliason, surgeons of the University Hospital, for their kindness in allowing us to secure the operative data reported in this paper from their records.

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LATE RESULTS OF SURGICAL TREATMENT OF PEPTIC ULCER BASED ON A STUDY OF 678 CASES.

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I. Introduction. There are few internists or surgeons at the present day who advocate the treatment of peptic ulcer by any single therapeutic measure; it is generally admitted that certain types of ulcer are best treated by medical therapeutics, others by surgical measures. Much of the confusion that has existed in the past in regard to the results of treatment by these two radically different methods has been due partly to the fact that both internists

and surgeons have been prone to draw conclusions after observing the results of their treatment over too short a period of time, and partly to the fact that patients who have been unsuccessfully treated by medical measures tend to gravitate to the surgeon, while the internist sees an unduly high proportion of the failures of surgery. To remedy this undesirable situation the Gastrointestinal Clinic* was organized several years ago (1923) at the Massachusetts General Hospital. In this Clinic the peptic ulcer cases are seen by a physician and a surgeon, who, not separately but together, arrive at a conclusion as to each individual case.

In all branches of surgery, as is natural and proper after a period of rapid technical development, emphasis is now being placed upon the late results of treatment. This is particularly important in surgery of the stomach and duodenum; no fundamentally new technical procedure has been introduced in this field for a considerable number of years, and sufficient time has therefore elapsed to evaluate the later results. The importance of the time element in estimating the efficacy of any operation has been, perhaps, the most valuable point brought out by the careful studies on the late result of surgical treatment of cancer, and has been considered of such significance that the term "cure" is there applied only with a qualifying clause as to the length of time which has elapsed since operation. The time factor is of the greatest importance also in estimating the late results of the surgical treatment of peptic ulcer, and is given detailed consideration in a later section of this report. There are, however, other and more complicated factors which make the results of surgical treatment of ulcer peculiarly difficult to judge, and a brief consideration of some of these factors is offered before presenting our findings.

Peptic ulcer is a disease of unknown etiology, characterized by spontaneous remissions and exacerbations of symptoms. The remissions are probably for the most part associated with the partial healing described by Crohn,[1] Mann[2] and others in their work on the process of healing in peptic ulcers; but there are many factors in the causation of symptoms from peptic ulcer that are not understood: the mechanism of pain sensations associated with ulcer, for example, is still a controversial point. It may safely be said that symptoms or lack of symptoms are often unreliable indications as to the condition of the ulcer, yet at the present stage of our knowledge they are our simplest and most reliable guides. Another factor which makes difficult the judgment of the late results of surgical treatment of peptic ulcer is the fact that the pathologic picture presents such widely differing aspects, varying from an ulcer that merely penetrates the mucosa and submucosa to one penetrating all coats and some adjacent organ, and from slight or no deformity

* This Clinic was organized by Dr. C. M. Jones and one of the authors; Dr. Jones was on leave of absence at the time this study was undertaken.

of the stomach or duodenum to the extraordinary picture presented by the so-called "hour-glass" stomach. The problem is rendered still more complex by the great number of types of procedure that may be employed in any given situation. In attempting to classify the results of the different operations, therefore, the number of cases comparable both as to pathology and as to surgical procedure must in many instances be small.

A further complication is introduced by the fact that operative procedures profoundly alter the physiology of the stomach and upper gastrointestinal tract, from the point of view both of the chemistry of the secretions and of the motor function. This altered physiology may result either in the formation of new ulcers* or in functional disturbances which may prove serious.

In setting forth our data we have made no attempt to oversimplify the problem, feeling that a detailed presentation of our findings will be of more value to the careful student of the subject than didactic conclusions which we ourselves might draw from our data.

Method. *Material.* This paper is based upon a study of 678 cases of peptic ulcer surgically treated in the Massachusetts General Hospital. The group includes the cases reported in 1922 by Scudder,[3] together with the cases of peptic ulcer operated upon from 1919 to 1923, inclusive. They fall into three main groups as follows:

Duodenal ulcers	393
Gastric ulcers	261
Gastric and duodenal ulcers	24
	678

Six hundred and fifteen of these patients were believed to be alive when this study was started.

Collection of Data. A letter was sent to each patient giving a definite appointment at the Gastrointestinal Clinic. One hundred and fifty patients responded in person to this request; 165 to a subsequent letter. All the remaining patients residing within a 10-mile limit of Boston whose letters were not returned "unclaimed" were visited; information concerning 42 cases was obtained in this way. Thus every patient in the community who could be traced through the postoffice was communicated with, in an effort to avoid any selection of cases. In 115 instances data were obtained from the hospital records of visits subsequent to operation. By these

* One of the most striking facts brought out by a review of the literature on the experimental production of acute ulcer in the duodenum or stomach is the uniform success which has attended all experimenters, whatever their method of procedure. This is due, undoubtedly, to the fact that ulcers readily occur in this highly specialized tissue following slight alterations in the physiology; there may be many different reasons why certain of these lesions become chronic.

various means we were able to collect information as to late results in 472 cases.

Classification of Results. Table I shows the main grouping of 393 duodenal ulcer cases and 261 gastric ulcer cases. We were unable to trace as long as two years after operation 68 of the duodenal cases, 66 of the gastric. Eighteen patients in the duodenal group and 15 in the gastric died one or more years after leaving the hospital and nothing, with one or two exceptions, is known of them beyond the mere fact of their death. In 30 cases in the duodenal group and 23 in the gastric group death followed operation. Two hundred and eighty duodenal ulcer cases and 159 gastric are analyzed for later results. Nineteen duodenal cases and 8 gastric had their first operation in another hospital; these are considered in the multiple operation group.

TABLE I.—ANALYSIS OF MATERIAL.

	Duodenal ulcer.	Gastric ulcer.
Cases not traced	68	66
Died one or more years after leaving hospital	18	15
Immediate mortality	30	23
Cases analyzed for later results	280	159
	396	263
Less number included under two headings	3	2
Total	393	261

In attempting to estimate the results of operation we have avoided the use of the words "cure" and "failure." Without precise knowledge, which is unattainable, as to the condition of the ulcer, the use of the word "cure" is obviously inaccurate; it is perhaps not too far-fetched to say that it is as little applicable here as in a consideration of the results of treatment of pulmonary tuberculosis. In regard to the term "failure," this can hardly be used in the case of the many patients who have a return of ulcer symptoms of differing degrees of severity after having experienced a number of years of comfort and well-being as a result of operation; the operation may even have been a life-saving procedure at the time it was carried out, and it is manifestly unjust to consider such an operation a "failure," even though the good effects may not be permanent. We have, therefore, contented ourselves with dividing the patients into "A," "B" and "C" groups, as described below, on the basis of symptoms shown during the period of postoperative observation.

Group A includes patients who showed no return of ulcer symptoms throughout the period of observation; their diet was wholly or approximately unrestricted. Patients of Group B either showed a recurrence of mild symptoms, referable to ulcer but easily controlled by slightly restricted diet, or experienced at least one period of short duration, during which the symptoms were of moderate

severity but were amenable to simple treatment. The patients were not incapacitated or restricted in their work, and the operation had undoubtedly been of great value to them. Patients of Group C experienced at some time following operation a recurrence so severe as to hinder them greatly in their work, to incapacitate them, or require further hospitalization.

Of the total number of cases of duodenal ulcer (261) followed for from two to ten years or more after operation, 172 (66 per cent) were classified as "A" throughout their period of observation, 40 (15 per cent) were classified as "B" and 49 (19 per cent) as "C." The corresponding figures for the 151 gastric cases were: "A," 104 (69 per cent); "B," 19 (12.5 per cent); "C," 28 (18.5 per cent). On the basis of these figures, it might be said that operation gave satisfactory results throughout the period of observation in about 81 per cent of the cases of gastric and of duodenal ulcer. This method of grouping, however, does not give sufficient importance to the time element: The cases followed for a shorter period of time show fewer recurrences than those observed over a more extended period, and an average is therefore misleading.

The problem thus arose as to a satisfactory method of classifying the patients who were symptom-free for a number of years and then showed a recurrence of ulcer symptoms. These were listed as "A" during the period of well-being and then listed as "B" or "C" during the remainder of the time followed. If the patient developed symptoms so severe as to demand a second operation he was accounted "C" during the total time the case was followed after the development of symptoms. For example, suppose for two years after operation a patient was symptom-free, then developed such a severe recurrence of symptoms as to require a second operation. Such a patient would appear as an "A" in the group observed two years after operation; he would then be counted as "C" throughout the remainder of his period of observation, for presumably without the second operation he would have continued to have trouble. The results of second operations are discussed later under the heading of "multiple operations."

Results. In Table II a detailed report of the cases followed from two to ten years is presented. The classification of the total group of duodenal ulcers (261) is given two years after operation; 232* of these cases are reported on four years after operation, 165 six years after, 105 eight years after and 64 ten or more years after. The corresponding group figures for the gastric cases are: 151 two years after operation, 136 four years after, 109 six years after, 77 eight years after and 51 ten or more years after. To the right of the column of figures showing the number of "B" and "C" patients is a statement as to the time the recurrence of symptoms took place.

* Twenty-nine of the 261 cases either had been operated on less than four years before this study was made or could not be traced after the two-year period.

TABLE II.—CLASSIFICATION OF CASES.

	Duodenal ulcer.	Gastric ulcer.
	Two Years After Operation.	
Group A	197	117
Group B	36 (31 showed recurrences within first year; 5 were "A" for 1 year)	16 (15 showed recurrences within first year; 1 was "A" for 1 year)
Group C	28 (22 showed recurrences within first year; 6 were "A" for 1 year)	18 (16 showed recurrences within first year; 2 were "A" for 1 year)
	261	151
	Four Years After Operation.	
Group A	171	105
Group B	28 (25 showed recurrences within first year; 3 were "A" for 1 year)	13 (12 showed recurrences within first year; 1 was "A" for 1 year)
Group C	33 (21 showed recurrences within first year; 5 were "A" for 1 year; 7 were "A" for 2 years)	18 (14 showed recurrences within first year; 2 were "A" for 1 year; 2 were "A" for 2 years)
	232	136
	*Six Years After Operation.**	
Group A	114	76
Group B	20 (15 showed recurrences within first year; 1 was "A" for 1 year; 4 were "A" for 4 years)	12 (9 showed recurrences within first year; 1 was "A" for 1 year; 2 were "A" for 4 years)
Group C	31 (15 showed recurrences within first year; 4 were "A" for 1 year; 7 were "A" for 2 years; 5 were "A" for 4 years)	21 (10 showed recurrences within first year; 1 was "A" for 1 year; 3 were "A" for 2 years; 7 were "A" for 4 years)
	165	109
	Eight Years After Operation.	
Group A	80	51
Group B	9 (8 showed recurrences within first year; 1 was "A" for 3 years)	11 (7 showed recurrences within first year; 1 was "A" for 1 year; 2 were "A" for 4 years; 1 was "A" for 6 years)
Group C	16 (6 showed recurrences within first year; 1 was "A" for 1 year; 4 were "A" for 2 years; 1 was "A" for 4 years; 4 were "A" for 6 years)	15 (6 showed recurrences within first year; 1 was "A" for 1 year; 3 were "A" for 2 years; 4 were "A" for 4 years; 1 was "A" for 6 years)
	105	77
	Ten Years After Operation.	
Group A	53	36
Group B	2 (Both showed recurrences within first year)	6 (5 showed recurrences within first year; 1 was "A" for 4 years)
Group C	9 (2 showed recurrences within first year; 1 was "A" for 1 year; 2 were "A" for 2 years; 2 were "A" for 6 years; 2 were "A" for 8 years)	9 (4 showed recurrences within first year; 3 were "A" for 2 years; 2 were "A" for 4 years)
	64	51
	(30 of these 64 cases were followed for more than 10 years, 3 of them developing severe symptoms)	(19 of these 51 cases were followed for more than 10 years; none of them developed symptoms)

Group A, symptom-free. Group B, mild symptoms. Group C, severe symptoms.

* The figures of the six-year group are shown in percentage form in Fig. 1.

It will be noted that about 11 per cent developed severe recurrences at the end of two years. In the cases followed four years the percentage of severe recurrences was about 14; in those followed six years, 19. After six years the percentages fall off somewhat, being 15 and 14 per cent for the cases followed eight or ten years; this is probably due to the fact that during this later period proportionately fewer of the cases developing severe symptoms could be traced. In the gastric cases the percentage of recurrences in the two-year, four-year and six-year groups was about the same as that for the duodenal ulcer cases. In the eight-year or ten-year groups it was somewhat higher, being about 19.5 and 17.6 per cent respectively.

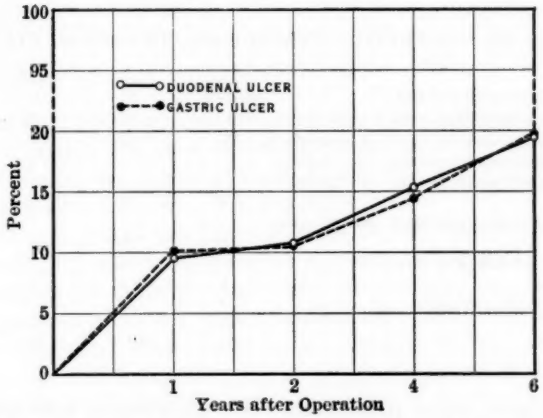

Chart I shows in percentage form the recurrences of severe symptoms that took place in the group followed for six years, and the time at which these occurred. See also Table II, cases followed six years.

In order to present in more detail the proportion of recurrences and the length of time after operation at which these occurred, the findings in regard to all the patients we were able to observe six years or more after operation which were given in Table II are also shown in percentage form in Chart I. This six-year group was selected because it consisted of a fairly large number of cases considered after a sufficient length of time had elapsed since operation to make a study of the results especially valuable. It will be noted in Chart I that while the greatest percentage of relapses occurred within the first year, there were many recurrences throughout the whole period of observation, so that at the end of six years about 19 per cent of both gastric and duodenal ulcer patients had developed severe symptoms, as against 11 per cent that showed recurrences at the end of the second year. In cases showing mild recurrences the symptoms appeared chiefly within the first year (Table II), the increase during the remainder of the six years being small.

Operative Procedures, Duodenal. In Table III the cases of duodenal ulcer are arranged according to the operation performed, the last three columns showing the groups in which these cases were finally placed on the basis of later symptoms. We see here that posterior gastroenterostomy formed the essential part of the operation in 230 cases, and was thus, either alone or in combination with other procedures, the major operative attack on duodenal ulcer. Of these 230 cases, 152 remained completely free from symptoms throughout the period of observation, and are placed in Group A; 37 showed mild recurrences at some time following operation. Definitely severe symptoms recurred in 41 cases; these cases were placed in Group C.

TABLE III.—OPERATIVE PROCEDURES, DUODENAL ULCER.

Operative procedure.	Total number.	Group A.	Group B.	Group C.
Posterior gastroenterostomy alone	147	92	28	27
Posterior gastroenterostomy + infolding	70	52	6	12
Posterior gastroenterostomy + excision	10	6	2	2
Posterior gastroenterostomy + pylorus ligature	3	2	1	..
Pylorectomy plus posterior gastroenterostomy	10	10	..	..
Excision or infolding of ulcer	16	6	3	7
Pyloroplasty	1	1	..	..
Pyloroplasty plus excision	4	3	..	1
Total	261	172	40	49

The 10 cases where pylorectomy was performed, with continuity of the intestine reëstablished by posterior gastroenterostomy, all appear in Group A. This operation was carried out for chronic ulcers situated near the pylorus and usually causing considerable organic obstruction of the pylorus. In 16 instances ulcers were excised or infolded without gastroenterostomy; of these, 14 were cases of acute perforation and will be discussed under that heading in a later section. Some type of pyloroplasty was carried out in 5 cases with good results in 4 instances.

Operative Procedures, Gastric. Table IV is similar in purpose to Table III and shows the operative procedures employed for gastric ulcers. It is interesting to note that of the small group of cases where posterior gastroenterostomy alone was performed, only 1 case showed return of severe symptoms. Posterior gastroenterostomy combined with infolding or excision of the ulcer was carried out in 72 cases, satisfactory results being obtained in 64 instances.

In 26 cases the ulcer was treated by infolding or excision alone, severe ulcer symptoms recurring in 12 instances or almost half the total number. These latter cases belong to the early period of development of knowledge concerning the surgical treatment of gastric ulcer, and serve to emphasize the soundness of the opinion

now current that excision of a gastric ulcer is unsuccessful in a large proportion of cases unless combined with a posterior gastroenterostomy.

TABLE IV.—OPERATIVE PROCEDURES, GASTRIC ULCER.

Operative procedure.	Total number.	Group A.	Group B.	Group C.
Posterior gastroenterostomy alone	24	20	3	1
Posterior gastroenterostomy + infolding	29	22	5	2
Posterior gastroenterostomy + excision	43	35	2	6
Excision alone	23	8	4	11
Infolding alone	3	2	..	1
Partial gastrectomy	17	12	2	3
Pylorectomy	4	3	..	1
Sleeve resection	4	1	2	1
Pyloroplasty	3	1	..	2
Gastrogastrostomy	1	..	1	..
Total cases	151	104	19	28

Partial gastrectomy or pylorectomy was carried out in 21 instances, with recurrence of severe symptoms in 4 cases.

Other operative procedures are listed, but their number is too small to furnish data of any importance.

Gastric and Duodenal Ulcer Present in the Same Patient. The operations performed on the 24* patients in whom there was an active lesion of both stomach and duodenum, were as follows: partial gastrectomy on 7, cuff resection on 1, posterior gastroenterostomy combined with excision or infolding of the ulcer on 13, anterior gastroenterostomy on 1, pyloroplasty on 1 and gastroenterostomy with gastroduodenostomy on 1. Three of these 24 patients died following operation; 8 we could not trace; 6 were observed for six years or more, 5 for three years or more and 2 for two years; of the 13 we were able to trace, 1 showed mild recurrence of symptoms and 12 remained symptom-free.

The late results of operation on this small group are strikingly good, perhaps because there was a large number of the more radical type of operation. The good results, however, are somewhat counterbalanced by the 3 deaths following operation. In 2 of these latter cases there was an hour-glass constriction of the stomach in addition to the duodenal ulcer; in the third case the inflammatory reaction around stomach and duodenum was so extensive that only an anterior gastroenterostomy could be carried out; this case developed a fatal obstruction during convalescence.

Operative Mortality. The factors governing the mortality rate following operation for peptic ulcer are complex. The outstanding circumstances that influence it are as follows: the age and general condition of the patient, the seriousness of the local pathology, the type of operation selected.

* In 8 other cases during operation for gastric ulcer the scar of a healed duodenal ulcer was found.

The causes of death following operations for duodenal and gastric ulcers are listed in Table V. There were 30 deaths in the duodenal series and 26 in the gastric. There were 4 deaths following operation for gastrojejunal ulcer, and these are included in Table V: 2 listed in the duodenal series and 2 in the gastric, according to the site of the primary ulcer. Six of the deaths followed operations for acute perforation: 5 duodenal and 1 gastric. The mortality, excluding these cases of acute perforation, was 6 per cent for the duodenal cases and 9 per cent for the gastric. The average age of these patients was a little over fifty years: 10 in the duodenal series and 8 in the gastric series were over sixty years of age.

TABLE V.—IMMEDIATE MORTALITY.

Causes of death.*	Duodenal ulcer cases.	Gastric ulcer cases.
Peritonitis	14	5
Pulmonary complication:		
(*a*) Pneumonia	4	8
(*b*) Pulmonary embolus	4	2
(*c*) Lung abscess	1	
(*d*) Gangrene of lung	1	
	—10	—10
Shock	2	3
Hemorrhage	2	3
Cardiac embolus	1	
Uremia	1	
Persistent vomiting	..	3
Fatty degeneration of liver	..	1
Septic parotitis	..	1
	— 6	—11
	30	26

* Four deaths following operation for gastrojejunal ulcer are included in this table: 2 listed in the duodenal series, 2 in the gastric, according to the site of the primary ulcer. Six of the deaths followed operations for acute perforations: 5 duodenal, 1 gastric.

The 6 cases of pulmonary emboli following operations for duodenal or gastric ulcers is a rather surprisingly large number when one recalls that the venous drainage from the operative field is into the portal system where emboli would be filtered out by the capillaries of the liver.

Among the fatal duodenal cases the ulcer was described as "penetrating" in 10 instances; the 2 deaths from hemorrhage belong in this group, the bleeding occurring from a deeply penetrating ulcer that could not be excised. One patient showed cirrhosis of the liver in addition to the ulcer. Among the fatal gastric cases a chronic perforation of the ulcer into the substance of the liver or pancreas was found in 4 instances. There was 1 hour-glass deformity. In 3 cases ulcers of both stomach and duodenum were present.

II. Acute Perforations. Of the total group of peptic ulcer cases, 39 had a history of acute perforations: 15 of the gastric ulcers and

24 of the duodenal ulcers. Of these, 7 had their first operation at another hospital and entered the Massachusetts General Hospital because of recurrence of symptoms; they are considered in the "multiple operations" group of cases. Of the 39, only 3 were females, 2 gastric and 1 duodenal.

In 3 of the 15 gastric cases the perforation occurred without any previous ulcer symptoms; in 1 case, after a few days of gastric distress. These 4 perforations were in patients under twenty-seven years of age. The average age of the remaining patients with perforated gastric ulcer was 43.6. The average duration of symptoms before perforation was 8.5 years.

Of the 24 duodenal perforations, 6 had only a few days of ulcer symptoms before the perforation occurred. Three of these cases were under twenty-seven years of age and 3 were thirty-six years or over; the age of the remaining cases in which the duration of symptoms before operation is recorded averaged 35.2 years. The average duration of symptoms was 7.4 years.

Contrasting the gastric and duodenal cases of perforation, it will be noted that in both there is a small group where perforation occurred either with no previous symptoms or after a very short prodromal stage. In the gastric group all such cases were in young persons; in the duodenal group half these cases were under thirty years and half were middle-aged or old.

Results of Operation for Acute Perforations. Thirty-two patients were operated on at the Massachusetts General Hospital at the time of an acute perforation, 6 of whom died following operation, giving an immediate mortality of 18.7 per cent. The cause of death in 5 of these cases was general peritonitis and in 1, hemorrhage.

Later results are known in 24 cases as follows: 7 of these cases had had infolding of the ulcer and posterior gastroenterostomy; of these, 6 had no recurrence during the five years they were observed; 1 had a recurrence of severe symptoms (perforation of a gastrojejunal ulcer) after seven years of well-being. In 17 cases an infolding of the perforation alone was carried out; of these, 11 had recurrence of severe symptoms, for the most part within the first year after operation; 3 had recurrence of mild symptoms; 3 had no recurrence during the six years they were under observation.

It is clear from the above figures that the prognosis in those cases where it is possible to perform a posterior gastroenterostomy as well as to close the ulcer is much better than in cases where only closure of the perforation can be carried out. It should be emphasized, however, that closure of an acute perforation is a life-saving procedure, and if a further operation is likely to add to the risk it should not be attempted. It is only in a small group of cases where the patient is in good general condition and is operated upon within a few hours of the perforation that anything more radical than a simple closure should be attempted.

Multiple Operations. Forty-nine cases were operated upon more than once; 4 of these were operated upon three or more times. In 22 instances the first operation was performed at the Massachusetts General Hospital; in 27 cases it took place at another hospital. Of the group of cases not given relief by operation, those that come to a second operation are of great interest because they afford an opportunity to determine accurately, in most instances, the exact nature of the pathology responsible for the persistent or recurrent symptoms.

Pathology Found at First Operation. Of the 49 cases coming to a second operation, 32 are believed to have shown duodenal ulcer at their first operation and 17 gastric. Of the 32 patients with duodenal ulcers, there were 10 whose first operation was for acute perforation; 2 patients with gastric ulcers had been operated upon for acute perforation; for more detailed discussion of these cases, see section on acute perforations. Of the remaining cases, there were 2 in which more than one ulcer was found in the duodenum at the time of the first operation; 2 in which more than 1 gastric ulcer had existed. It is interesting to note that in 5 instances the duodenal ulcer found at the first operation was described as "small." Among the gastric cases there was 1 in which the stomach showed an hourglass deformity. There was nothing outstanding in the pathology described for the remaining cases.

Symptomatic Relief following First Operation. The average period of symptomatic relief following the first operation was about one and a half years for the duodenal group and about half as long for the gastric. Four patients in the duodenal group remained symptom-free for six years or over, and then developed severe symptoms. A gastrojejunal ulcer was found at the second operation in 3 of these cases. The fourth case was of special interest: the first operation had disclosed multiple ulcers of the duodenum, and a posterior gastroenterostomy was performed; the patient was without symptoms for ten years and then developed severe symptoms requiring the second operation, which revealed the fact that the duodenal ulcers had healed and that the later symptoms were due to a large ulcer of the lesser curvature of the stomach.

The average time period between the first and second operation was about four years for both groups; there were 9 instances in which the interval was seven years or more.

In the great majority of cases (43) the chief symptom that brought the patient to a second operation was pain. In 5 instances the presenting symptom was hemorrhage and in 1 instance, vomiting.

The Second Operation. Of the 49 cases requiring further surgical treatment, a gastrojejunal ulcer was found at the second operation in 14 instances. In 9 instances the posterior gastroenterostomy had been carried out for duodenal ulcer and in 5 instances for gastric. In 6 cases with gastrojejunal ulcer the gastroenterostomy had been performed at the Massachusetts General Hospital. Since there

were 357 posterior gastroenterostomies performed in this series in which late results were noted, the instances of proven gastrojejunal ulcer form 1.7 per cent. For the most part the procedure employed at the second operation consisted in resection of the ulcer and stoma; in some instances a new posterior gastroenterostomy was performed. There was 1 case in which an exploratory operation only was carried out, the general condition of the patient not permitting a radical operation; in another patient the only procedure carried out was the closure of a perforation. Among the 14 cases of gastrojejunal ulcer there were 4 deaths. The late results of operation on the other 10 cases were in the great majority of instances decidedly poor. For more comprehensive and detailed accounts of certain of these patients, a recent article by Davis[4] should be consulted.

Of the remaining 35 cases requiring a second operation, the first operation had been for duodenal ulcer in 23 instances and for gastric ulcer in 12.

In 10 of the 23 duodenal ulcer cases posterior gastroenterostomy did not constitute part of the first operation; the recurrent symptoms in all of this group were due to a chronic duodenal ulcer. In 6 of these 10 cases (4 of which were followed six years or longer) a posterior gastroenterostomy at second operation gave good results; in 1 instance the patient died following the operation; in 2 the late results are unknown; in 1 the late results were poor.

In 13 of the 23 cases where the first operation was for duodenal ulcer a posterior gastroenterostomy had constituted the major part of the original procedure. In 8 of the 13 some abnormality other than gastrojejunal ulcer was described as having developed in connection with the posterior gastroenterostomy: "stenosis," "adhesions," "poorly placed," etc.; in 6 of these 8 a chronic ulcer of the duodenum also existed; in 2 the ulcer had apparently healed, the symptoms presumably being due to the malfunction of the enterostomy. In 5 of the 13 cases the gastroenterostomy performed at first operation was satisfactory, the later symptoms being due in most instances to chronic duodenal ulcer usually complicated by "dense adhesions;" 1 case showed that the duodenal ulcer had healed and a gastric ulcer had formed.

The procedures at second operation on the above group of 13 were varied and the results in most cases disappointing. There were 2 pylorectomies, 1 giving good results for six years, the other giving moderately good results. There was 1 gastric resection, result unknown; 2 pyloroplasties, result unknown; lysis of adhesions in 2 cases, followed by recurrence of symptoms. The posterior gastroenterostomy was disconnected in 5 instances, with poor results twice, with moderate success once, and with result unknown twice. One excision of a gastric ulcer gave good results for five years.

In 9 of the 12 cases in which the original operation was for gastric

ulcer no posterior gastroenterostomy had been carried out at the first operation: the activity of the old ulcer was responsible for the recurrence of symptoms in 3 of these; obstruction at the pylorus from the old ulcer in 2; a new gastric ulcer had formed in 3 cases, the original ulcer having been excised; in 1 instance a duodenal ulcer had formed. Eight of these cases were treated by posterior gastroenterostomy; 1 by partial gastrectomy. The immediate results were good in all instances; 2 of the cases which were treated by posterior gastroenterostomy showed a recurrence of symptoms after one and two years, respectively; the others, 3 of which have been followed four years or more, have shown no recurrence.

In 3 of the 12 cases in which the first operation was for gastric ulcer, a posterior gastroenterostomy formed a part of the procedure. In 2 of these 3 a chronic gastric ulcer was responsible for the recurrence of symptoms. One of these was complicated by an hour-glass deformity: an anterior gastroenterostomy was performed, but the patient did not survive the operation. In the second case it was not possible to carry out any radical procedure: a drain was placed to the region of an inflammatory mass on the lesser curvature; the patient improved after the operation but died two years later. The third case showed a twist of the jejunum near the gastrostomy opening: the posterior gastroenterostomy was disconnected and a Roux operation carried out; the patient was symptom-free during the two years he was followed.

III. Factors Affecting Prognosis and Choice of Operation. In order to see if any guide could be obtained for the selection of cases suitable for operation, or any prediction be made as to the outcome of operation, an attempt was made to correlate the late results of the operation with the preoperative and operative findings.

The patients were divided as before into "A," "B" and "C" groups. The following points were than tabulated for the several groups: the ratio of male to female; the average age of patients; the duration of symptoms before operation; the presence or absence of six-hour residue as shown by Roentgen ray examination; the average total acidity; the location and size of the ulcer. The appendectomies performed in connection with operations for duodenal ulcer were also tabulated. The results are set forth in Table VI.

The Ratio of Male to Female Patients. Duodenal ulcer, it is generally agreed, occurs about four times as often in males as in females. This ratio was found to hold true in all three groups of patients ("A," "B" and "C"). This is an interesting fact, for the differences in mode of life and occupation of men and women might be expected to exert some influence on the recurrence of symptoms. In the gastric cases a striking difference between the sexes is shown in regard to the recurrence of symptoms, for while the ratio of sex in patients that remained symptom-free or developed

only mild symptoms is 1 to 1, four times as many males as females developed severe recurrence of symptoms. The reason for this is not clear.

Average Age of Patients and Duration of Symptoms Before Operation. It will be noted that in the duodenal ulcer cases the patients who remained symptom-free following operation averaged two and a half years older at time of operation than those who developed mild symptoms, and seven years older than those who developed severe symptoms. It will also be noted in the duodenal cases that the duration of symptoms before operation was longer in the cases that had no recurrence of symptoms than in the other two groups.

These findings in regard to the age of the patients and the duration of preoperative symptoms confirm the current opinion that it is desirable to treat cases of duodenal ulcer by medical therapeutics as long as possible, not only because a certain number of cases will be cured by that means, but also because the results of operation will be definitely better in a chronic ulcer of long standing.

The patients with gastric ulcer when thus analyzed show a marked contrast to the patients with duodenal ulcer. The average age of the gastric patients at the time of operation was practically the same in the "A," "B" and "C" groups. The duration of symptoms before operation was shorter in the cases that had no recurrence of symptoms than in the other two groups. These figures indicate that postponing operation did not result in a more favorable outcome.

Six-hour Residue. In the duodenal ulcer cases, considerable six-hour retention of bismuth was noted in 72 instances; it was absent or slight in 161 examinations. As shown in Table VI, 58 of the 72 cases appear in Group A, 6 in Group B and 8 in Group C. It is interesting to find such a large proportion listed in the group showing no recurrence of symptoms. It has been noted for a long time in the literature that patients showing obstruction from duodenal ulcer formed a particularly favorable group for surgical treatment, thus leading Eiselsberg[5] and others to advocate deliberate closure of the pylorus, by fascial tie or other procedure, in addition to a posterior gastroenterostomy. The results of this procedure have been adversely criticized by many writers. The suggestion is here made that the reason so many cases that showed stasis in our series obtained good results from operation was due not to the obstruction of the pylorus *per se*, but to the fact that the lesions causing marked obstruction are chronic, indurated lesions, the type which yields best to surgical treatment.

Gastric stasis in the presence of gastric ulcer was noted in 67 instances. As shown in Table VI, it was found 48 times in cases placed in Group A, 7 times in those of Group B, 12 times in those of Group C, which consisted all-told of only 28 cases. Thus, while it was often present in cases remaining symptom-free, it was also

found in a high proportion of the cases later developing severe symptoms.

TABLE VI.

	Duodenal ulcer.			Gastric ulcer.		
	Group A.	Group B.	Group C.	Group A.	Group B.	Group C.
Ratio of males to females	4 to 1	4 to 1	4 to 1	1 to 1	1 to 1	4 to 1
Average age in years	42	39.5	35	45.5	46	46
Average duration of symptoms before operation, in years	7.7	6.5	4.8	6.7	12	8
Six-hour residue	58	6	8	48	7	12
Average total acidity, cc. N/10 solution	63.7	48	58.7	54	52	56
Location of ulcer:						
Anterior surface	..	..	..	4	0	1
Posterior surface	..	..	..	10	1	3
Lesser curvature	..	..	..	72	8	24
Near the pylorus	..	..	..	21	3	3
First portion	135	34	29	..	..	..
Second portion	8	1	1	..	..	..
Size of ulcer:						
Large	34	8	5	..	..	..
Small	18	8	11	..	..	..
Appendectomies performed on duodenal ulcer cases, per cent	20	11	25	..	..	..

The Average Total Acidity. The average total acidity was within normal limits in both duodenal and gastric ulcer cases and showed little variation in the "A," "B" and "C" groups. In view of the stress that has been laid on the rôle of acid in causing recurrence of ulcer symptoms after operations, it is striking that in the patients with duodenal ulcer who later had recurrence of symptoms, the total acidity before operation averaged slightly lower than it did in the patients who remained symptom-free. It is interesting, however, that of the 6 cases (4 duodenal and 2 gastric ulcers) later developing gastrojejunal ulcers, the total acidity before the first operation was recorded in 5 instances, and in each case a definitely high value was found.

Location of the Ulcer. In the great majority of cases the duodenal ulcer was described as located in the first portion of the duodenum. This is true for all three groups. About two-thirds of the gastric ulcers were described as occurring on the lesser curvature. The next largest number was described as occurring in the region of the pylorus. No important relation is brought out by our figures between the location of the ulcer and the results of operation.

Size of the Ulcer. It is interesting to note (Table VI) that in the group of patients with duodenal ulcer who developed severe symptoms after operation (Group C) the ulcer was described as "small" almost twice as many times as "large;" while in the group that remained symptom-free (Group A) the reverse was true.

This brings out again the point that the large, callous, duodenal ulcer is the more favorable type for operation.

Effect of Appendectomy. Since Balfour[6] has stressed the importance of infections of the appendix as an etiologic factor in the recurrence of ulcer symptoms, it is interesting to note (Table VI) that removal of the appendix did not in this series seem to lessen the recurrence of ulcer symptoms, the groups showing such recurrences having had a higher percentage of appendectomies (36 per cent) than the group showing no recurrences (20 per cent).

Summary. This study is based upon 678 cases, grouped as follows: 393 duodenal ulcers and 261 gastric ulcers; 24 gastric and duodenal ulcers in the same patient. In 472 of these cases information was obtained as to the condition two or more years after operation.

About 11 per cent of the duodenal ulcer patients showed a severe recurrence of symptoms by the end of two years, 14 at four years, 19 at six years, 15 at eight years and 14 at ten years. The figures for the gastric cases were about the same, except that the percentage of recurrences in the eight- to ten-year groups was somewhat higher —19.5 and 17.6 respectively. The results in the cases of gastric and duodenal ulcer in the same patient are given in detail in the text; in general they were good.

Excluding the cases of acute perforation, the operative mortality was 6 per cent for the duodenal ulcer cases and 9 per cent for the gastric. The average age of the patients dying after operation for duodenal ulcer was fifty-one, 10 being over sixty years of age; of the gastric patients, fifty, 8 being over sixty years of age.

Section II deals with acute perforations and multiple operations. Twenty-four of the duodenal patients and 15 of the gastric patients had a history of acute perforation. The average duration of symptoms before the perforation was about eight years; but there were a few cases where the perforation occurred with brief, if any, previous symptoms. In the gastric group all such cases occurred in young persons; whereas in the duodenal group half were in middle-aged or elderly persons. The immediate mortality was 18.7 per cent. The late results show that the prognosis in the small group where it is possible to perform a gastroenterostomy as well as to close the perforation, is much better than in cases where closure alone is possible. It is emphasized, however, that closure of an acute perforation is a life-saving procedure, and if further operation is likely to add to the risk it should not be attempted.

Of the 49 cases having more than one operation, 32 are believed to have shown duodenal ulcers at their first operation and 17 gastric. The duration of symptomatic relief following the first operation averaged about one and a half years for the duodenal group and a little less for the gastric. The average time period between the first and second operations was about four years. In the great majority of cases (43) the chief symptom that brought the patient

to a second operation was pain; in 5 cases the presenting symptom was hemorrhage; in 1 instance, vomiting.

Among the cases twice operated upon, a gastrojejunal ulcer was found in 14 instances; in 6 of these the gastroenterostomy had been performed at the Massachusetts General Hospital and shows 1.7 per cent of proven gastrojejunal ulcers among the cases from this hospital. The results of the operation for gastrojejunal ulcers were in the great majority of cases poor.

Of the remaining 35 cases requiring a second operation, approximately half had no gastroenterostomy at their first operation. A gastroenterostomy at the second operation gave in general excellent results. In the group where a gastroenterostomy constituted part of the first operation the results of the second operation were usually disappointing (see text).

Section III describes an attempt to correlate the preoperative and operative findings with the late results. The following points were brought out:

A greater proportion of the men than of the women with gastric ulcer developed severe recurrence of symptoms; this did not hold true for duodenal ulcer patients (Table VI). The younger patients with duodenal ulcer showed a higher incidence of recurrence than did the older group. The average duration of symptoms before operation in duodenal cases was almost twice as long in the patients who remained symptom-free as among those who showed severe recurrences, indicating clearly that an ulcer of long standing responded more favorable to operation. In the gastric cases no inference as to late results could be drawn from the age of the patient or the duration of symptoms before operation.

The results of operation in the duodenal ulcer group were better in those cases that showed evidence of gastric stasis prior to operation. The suggestion is made that this is not due to obstruction of the pylorus *per se*, but to the fact that marked obstruction is caused by chronic, indurated lesions—the most favorable type for operation. No relation could be found between the total acidity prior to operation and the later development of symptoms, except that the patients who later developed gastrojejunal ulcer showed a high acidity prior to the first operation. The small ulcer of the duodenum showed a greater recurrence of symptoms than the larger, calloused ulcer.

Removal of the appendix in connection with the operation for duodenal ulcer did not, in this series of cases, appear to lessen the recurrence of ulcer symptoms.

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A COMPARISON OF THE LATE RESULTS OF AMBULATORY AND HOSPITAL TREATMENT OF PEPTIC ULCER.*

By John M. Blackford, M.D.,
and
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In 1926 we reported[1] a statistical and diagnostic study of 250 patients suffering from peptic ulcer (gastric 44 cases, duodenal 206 cases). We noted particularly then that our clinical diagnostic errors, apparently proved by operation on 90 patients, were 4.5 per cent, and that we believe our diagnoses in the unoperated cases were as accurate as in those operated upon. We also noted that half of our patients suffering from duodenal ulcer dated the onset of their symptoms before the age of twenty-five years, while only one-fourth of gastric ulcer patients placed the onset of symptoms before the age of twenty-five years. The average duration of gastric ulcer symptoms before consulting us had been only half the duration of symptoms of those suffering from duodenal ulcer. A history of massive hemorrhages was obtained from 15 per cent of the patients suffering from duodenal ulcer, and from 30 per cent of the patients suffering from gastric ulcer. Acute perforation occurred in nearly 6 per cent of all patients.

From these 250 patients have now been selected those suitable for follow-up study of medical results; attempting to ascertain, by careful inquiry, the present condition of all patients who were advised regarding medical treatment. We have found few statistical studies in medical literature on the late results of hospital medical treatment and no figures whatever on the late results of ambulatory treatment of peptic ulcer.

What are the results of medical treatment for peptic ulcer? The literature is rich in estimates of from 60 per cent to 90 per cent of cures by medical means, but there are remarkably few articles from which accurate conclusions, ascertained by follow-up study after years, can be obtained. Most authors have stressed the importance of hospitalization for three or four weeks and very careful supervision up to a year or more after leaving the hospital.

The noteworthy work of Sippy has, strange to say, never had a follow-up study by himself or his coworkers. Other clinicians using Sippy's method, particularly Jones,[2] Phillips,[3] White,[4] and Shattuck,[5] have not approached Sippy's claimed percentage of cures. Smithies[6] has reported a series of 470 cases treated by his

* Read before the American Gastro-enterologic Association at Washington, D. C., April 30, 1928. From the Virginia Mason Hospital.

own method, in which he states there is a "cessation of the ulcer process" in 77 per cent.

As far as we can learn, there are no published results of ambulatory treatment, except that White[4] states that his cases of duodenal ulcer have often been treated by ambulatory methods. Ambulatory treatment is recognized as good by Alvarez,[7] Rehfuss,[8] and others; but no results have been published.

It is strange that internists have not been more active in the follow-up study of patients suffering from peptic ulcer. Surgeons have set a good example in this field. Balfour[9] has reported 1000 cases after gastroenterostomy for duodenal ulcer, and shows 88 per cent of good results after ten years; the 12 per cent remaining manifestly does not include his remote mortality from ulcer or other causes. Various other surgeons have published good results, and our own experience confirms the observation that gastroenterostomy, when successfully done, gives a high percentage of clinical cures. For this reason we have had far more than the average internist's leaning toward surgical treatment for ulcer.

MEDICAL TREATMENT. Our interest in peptic ulcer goes back some eighteen years. Training in a large surgical clinic, where peptic ulcer was usually treated surgically, made us feel that such treatment was usually the procedure of choice. On entering private practice in 1917, we began to find that patients who refused operation often did well on ambulatory treatment of the casual kind. We put a number on bismuth and magnesia tablets or other alkalies, frequent feeding, and reasonable care of diet. Such patients did well as a rule; but occasional failures and Sippy's brilliant writings caused us to put some 30 selected patients under hospital management between 1920 and 1923.

Patients advised hospital treatment were a selected group. They were selected for such treatment because they were intelligent, younger than the average, anxious to coöperate, and without surgical complications. This selection gave as an average patient a male, aged thirty-one years, with a history of periodic trouble for seven years. Such patients were treated as accurately as possible, both in the hospital and afterward.

Hospital treatment almost always brought immediate relief; but as time elapsed we found that many patients had a return of trouble, in spite of every care and advice that we could give them regarding diet and medication. We were forced to the opinion that it was doubtful whether these favorable cases (with three or four weeks of training in the hospital behind them and a year or more of extreme care afterward) did better than those on casual ambulatory treatment.

This impression became so definite that since 1923 we have practically given up hospital medical treatment. Since that date we have treated medically in the hospital only patients too ill to be on their feet.

Those patients, therefore, who were advised ambulatory treatment more than five years ago were usually in one of two groups: either unable to take medical treatment in the hospital, or they requested ambulatory treatment for temporary relief with the idea of later coming to operation. Several of the latter group, whom we felt rather urgently surgical, had so much relief that they now consider themselves free from trouble. In the past five years we have usually advised ambulatory treatment in cases of uncomplicated duodenal ulcer and in a very few cases of gastric ulcer.

The treatment advised has been simple and has emphasized frequent feedings. We have advised a relatively smooth diet, avoiding highly seasoned foods, fried foods, and notably indigestible foods. We have cautioned against overloading the stomach and against irregular hours. We have advised about the hygienic care of the bowels. We have usually advised bismuth and magnesia tablets or other alkalies an hour after meals; though patients have often discontinued such medication of their own accord, to resume medication later if there were any suggestion of trouble. Each patient has been given a talk on the importance of proper living, on the avoidance of mental stress and worry, and on the evils of tobacco and alcohol for the ulcer patient. We have laid most emphasis, however, on frequent feedings; and this is usually reported by the patient to be the most valuable feature of the treatment, rather than the kind of food or drug. We have done our best to avoid making invalids or neurasthenics of our patients. They have had no period of bed or hospital treatment, and they have continued in their usual occupation.

Such measures have given so much relief that the majority of patients have considered themselves entirely relieved.

Results of Medical Treatment. We have interviewed or obtained written reports from two-thirds of all patients upon whom we have not actually operated. We then excluded from this study those who left us to seek operation elsewhere, or those who were diagnosed as having complicating diseases requiring operation, particularly gall-bladder disease or appendicitis.

Approximately 100 patients were left available for study, who had had a diagnosis made of peptic ulcer two to ten years ago, and had been given instructions regarding medical treatment.

We carefully reviewed these 100 case histories with their Roentgen ray and laboratory findings, and excluded each case in whom there was any doubt regarding the clinical diagnosis. This left 86 patients (6 gastric ulcer, 80 duodenal ulcer) in whom we feel sure of the diagnosis (allowing 5 per cent or less for clinical error). In other words, we believe that an indurated chronic ulcer existed in each of the 86 cases considered.

The study includes all patients to whom medical advice was given. Nearly half of these patients were advised operation, but insisted on

trying medical treatment. These 86 patients are cases on whom we would have urged operation prior to 1917; they would usually have had gastroenterostomy done and be now in a postsurgical group.

PEPTIC ULCER.

Percentage Results following Hospital Treatment.

G. U.	D. U.	Cases.	Authors.	Years.	Satisfactory.	Improved.	No relief.	Operated.	Dead.
4	26	30	Jones	1– 5	60.0				
6	22	28	Shattuck	½– 2	78.5	..	10.7		
	152	152	White (many amb.)	3– 5	57.0	21	4.0	16	
128	342	470	Smithies	2–10	77.0	("Cessation ulcer process")			
	20	20	Blackford	2–10	60.0	15	5.0	15	

Percentage Results following Casual Ambulatory Treatment D. U.

		33	Blackford	5–10	55	12	6	15	12
		27	Blackford	2– 5	63	11	11	4	11
		60	Blackford	2–10	58	12	8	10	12

SUMMARY. RESULTS AFTER TWO TO TEN YEARS. TREATMENT OF PEPTIC ULCER.

(80 Duodenal ulcers: 6 Gastric ulcers.)

86 Medical Cases. (Blackford):	Per cent.
50 Satisfactory	58.1
12 Improved	14.0
7 Unimproved	8.1
9 Operated	10.5
2 Died from ulcer	2.3
6 Died from other causes	7.0

(78 Duodenal ulcers: 25 Gastric ulcers.)

103 Surgical Cases. (Mason):	Per cent.
75 Satisfactory	72.9
15 Unsatisfactory	14.5
8 Excision of ulcer	
7 After gastroenterostomy	
6 Immediate and remote mortality	5.9
7 Deaths from other causes	6.7

Average age:	Years.
Hospital patients	31
Ambulatory patients	41
Whole group	37
Average duration of symptoms:	
Hospital patients	7
Ambulatory patients	12
Whole group	11

Patients over 65 omitted.

Gastric Ulcer. Only 6 of 44 cases can be included, because the rest have been operated upon in our clinic or by other surgeons. On ambulatory treatment, 3 are practically free from trouble, 2 are somewhat improved, and the other patient, a very old man, is utterly miserable.

Duodenal Ulcer. Eighty cases are available for study; 60 received casual ambulatory treatment and 20 had most careful hospital management and after care as advised by Sippy. Operation was advised for half of the 80 patients, but was refused in favor of a trial on medical management.

Hospital Treatment. Twenty patients show an average age of thirty-one years, with an average history of seven years. Treatment has given satisfactory results in 60 per cent, with some improvement in 15 per cent more. Fifteen per cent have come to operation on account of the failure of medical treatment or of dissatisfaction with it. No relief whatever was obtained in 5 per cent. Seventeen patients out of 20 were treated more than five years ago. One fatality occurred while the patient was taking Sippy treatment, but it is not included here because the patient was not under treatment in the hospital.

Ambulatory Treatment. Sixty patients are available for this study, approximately half treated more than five years ago. Results of follow-up study show that 58 per cent gave satisfactory results, with 12 per cent more who are improved. Eight per cent have had no relief. Ten per cent have come to operation. Twelve per cent are dead.

The average age of this ambulatory group is forty-one years, with an average history of disease of twelve years. Thus we see that results in a less favorable class of patients, averaging ten years older and with a history five years longer than those in the hospitalized group, give practically the same percentage of relief as those treated by hospitalization.

Hemorrhages. Massive hemorrhages during or after treatment have occurred in 5 patients, 2 of whom died from hemorrhage.

The first fatality was a man, aged fifty-three years, with a history of duodenal ulcer for many years. Three years before coming to us he had had a successful operation elsewhere for rectal carcinoma. Stomach symptoms forced him to seek relief and he was placed on a Sippy management at home. He died suddenly on the eighteenth day of Sippy treatment from massive hemorrhage. The second fatality was a man, aged eighty-one years, with a history from youth quite typical of duodenal ulcer. He was placed on ambulatory treatment with complete relief for a year. Then prostatectomy was undertaken elsewhere and he died suddenly on the fifth postoperative day from a massive gastric hemorrhage.

Two of the remaining 3 patients had had hospital management.

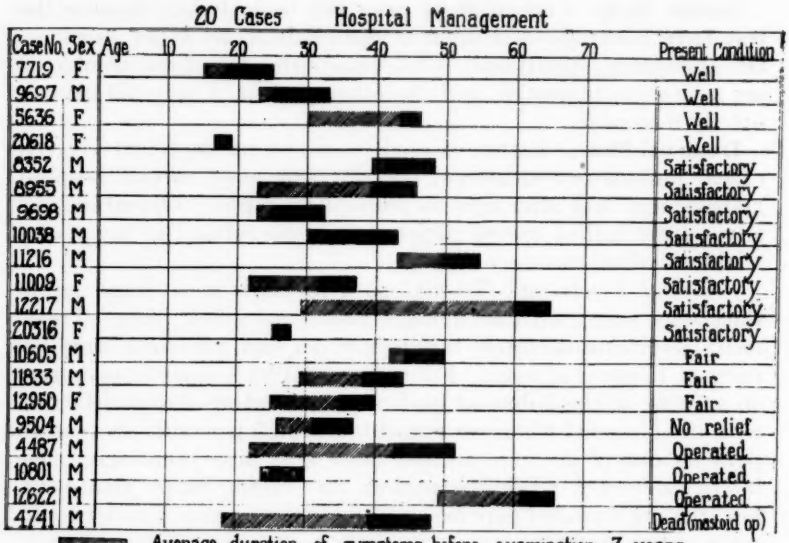

CHART I.

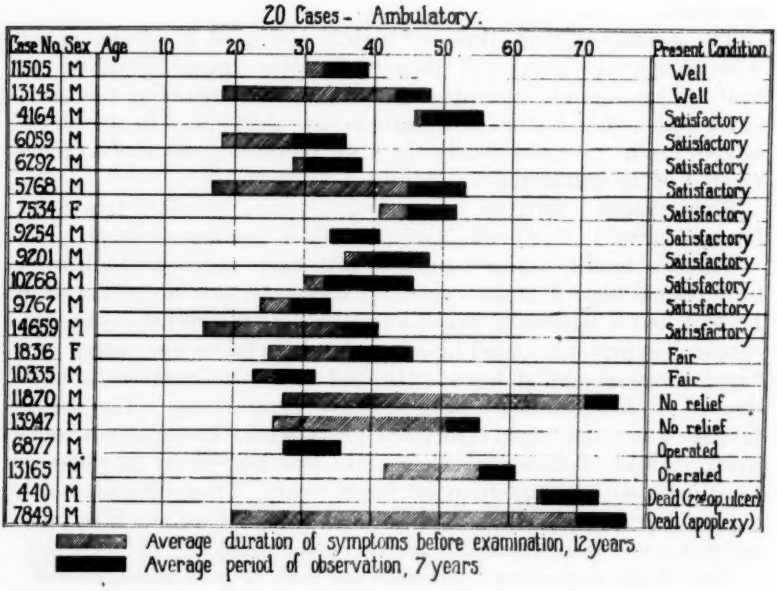
20 Cases - Ambulatory.
Case No. Sex Age 10 20 30 40 50 60 70 Present Condition
11505 M Well
13145 M Well
4164 M Satisfactory
6059 M Satisfactory
6292 M Satisfactory
5768 M Satisfactory
7534 F Satisfactory
9254 M Satisfactory
9201 M Satisfactory
10268 M Satisfactory
9762 M Satisfactory
14659 M Satisfactory
1836 F Fair
10335 M Fair
11870 M No relief
13947 M No relief
6877 M Operated
13165 M Operated
440 M Dead (perf. op. ulcer)
7849 M Dead (apoplexy)
Average duration of symptoms before examination, 12 years.
Average period of observation, 7 years.

CHART II.

Mortality. Nine patients whom we have treated for ulcer are dead. Two died from ulcer hemorrhage, as just related. Seven died from causes not related to ulcer or its complications.

It is worth mentioning that we have had one fatality from an appendiceal abscess which developed years after a gastroenterostomy. Two other patients had hospital medical treatment and subsequently required operation for appendicitis.

Acute Perforation. We have no knowledge that acute perforation has occurred in any patient to whom any kind of medical treatment has been advised.

SURGICAL INDICATIONS. Peptic ulcer with complications is best treated surgically. Obstruction, perforation, repeated massive hemorrhages, extreme pain indicating chronic perforation, and perigastric inflammation are surgical conditions. Recurring attacks of appendicitis or accompanying gall bladder disease are likewise indications for surgery. We have found that most of our gastric ulcer patients have required operation by others if not done by our clinic; hence we have usually advised surgery for gastric ulcer. The laboring man and the unintelligent foreigner suffering from peptic ulcer are usually unable to coöperate in treatment, hence we usually advise operation for them. These ideas, which we believe we share in common with a large part of our profession, have led to operation on most patients suffering from gastric ulcer and on about 40 per cent of patients suffering from duodenal ulcer.

Results of Surgical Treatment. Mason[10] has recently reported results of surgical treatment of peptic ulcer in more than 100 of our patients. His percentage results are practically identical with our medical figures. We recognize immediately, however, that his patients include the patients who had complications, include our bad medical results, and include patients who had had trouble for many years. We can say that the patients operated upon in our clinic average greater severity of symptoms than those treated medically. The surgical results are, therefore, more credit to the surgical treatment.

REMARKS. We feel apologetic about presenting only 20 hospital cases for consideration; yet if we add to them the series reported by Jones[2] and that reported by White,[4] we have 200 cases, with identical percentage results; and 200 patients make a group large enough to allow at least some conclusions to be drawn. We believe that 60 cases followed after ambulatory treatment are a sufficient number to permit us to draw conclusions.

Though not a constant procedure, we have reëxamined many of our patients. We have repeatedly confirmed the now well-known fact that most clinically cured ulcers still show Roentgen ray findings typical of ulcer.

Mortality from causes not related to ulcer is no reason to presume the failure of ulcer treatment. If 70 per cent of the reported 9 deaths

were added to 60 per cent of good results and 10 per cent of cases reporting improvement, then we can state that 7 per cent plus 10 per cent plus 60 per cent gives 77 per cent in which medical treatment has been justified—and some statistics have been thus built up.

There are no figures on what happens to untreated peptic ulcer, but undoubtedly many ulcers are unrecognized and yet their possessor lives to old age. The physician sees only the patients having enough trouble to bring them to him for relief.

The evaluation of results in a follow-up study is after all the patient's interpretation of results, whether he has been treated surgically or medically.

CONCLUSIONS. These observations after a period of two to ten years have shown:

1. Casual ambulatory medical treatment has been satisfactory in 60 per cent of uncomplicated cases of duodenal ulcer.

2. Careful Sippy management has likewise been satisfactory in 60 per cent.

3. Hospital medical treatment has not given better results than ambulatory treatment. Hospital treatment may better train the patient to look after himself, yet the results have not been better for the patient.

4. Serious hemorrhage during or after medical treatment has occurred in 6 per cent (5 out of 80 cases).

5. No instance of perforation is known to have occurred during or after any kind of medical advice.

6. A mortality of 2 per cent (2 cases) attributable to ulcer hemorrhage has occurred in follow-ups for from two to ten years. Both cases were notably poor risks that would not have been considered surgical by the most enthusiastic surgeon.

7. Hemorrhages have not been prevented by either medical or surgical treatment. They have occurred after medical or surgical treatment with the same percentage of frequency. Repeated hemorrhages indicate a resection of the ulcer-bearing area.

8. Complications of peptic ulcer are best treated surgically. Such cases give the best surgical results and the poorest medical results.

9. Our medical cases cannot be considered to parallel in severity the surgical cases. The surgically treated ulcer cases include the bad medical results, the complications, and the very severe cases.

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THE EFFECT OF SMALLER DOSES OF HISTAMIN IN STIMULATING HUMAN GASTRIC SECRETION.*

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Histamin has been demonstrated beyond question to be a stimulant to gastric secretion; and experiments have shown further that this drug may be used as a possible aid in differentiating between true and pseudoachylia.[1] Since 1925, many contributions have appeared in the literature on the subject and its related phases.

A review of the experiments dealing with the action of histamin on man shows that in practically all of the tests hitherto conducted, the dosage employed has ranged from 1 mg. to 1.50 mg. or more. That these quantities may be unduly large is suggested by the reports of unpleasant or even severe reactions following the subcutaneous injections of the doses used.

Accordingly, we deemed it important to ascertain whether the dosage of histamin could be diminished so as to avert unpleasant symptoms or at least reduce them to a minimum without entirely impairing the efficacy of histamin as a gastric stimulant. This seemed the more important because no attempt appears to have been made hitherto to determine precisely within what ranges effective dosage lies.

In the present study, emphasis has been placed upon the dosage factor rather than upon other features of the secretory response of man to histamin hydrochlorid.

The human subjects selected for observation averaged 160 pounds in body weight. Each subject reported in the morning before breakfast, so that the fasting stomach contents could be extracted. Particular attention was devoted to any systemic reactions that could be detected. A record was taken of blood pressure and pulse rate. The subjects were then given subcutaneous injections of histamin, whereupon the observations of blood pressures and pulse rate were further taken at the end of five, ten and fifteen minutes; and thereafter at fifteen-minute intervals. Simultaneously samples of gastric contents were removed by the aid of an Einhorn or Rehfuss tube at fifteen-minute periods. The material thus removed was measured; the free hydrochloric acid and total acidity determined and expressed in terms of cubic centimeters of tenth normal acid. Furthermore, the total volume of the secretion during

* Read before American Gastro-enterological Association, May 1, 1928, Washington, D. C.

the intervals was also ascertained. The subjects were not permitted to swallow saliva and were made to expectorate into vessels designated for such purpose. Some subjects were also given a standard test meal of one shredded wheat biscuit and 200 cc. of water. This

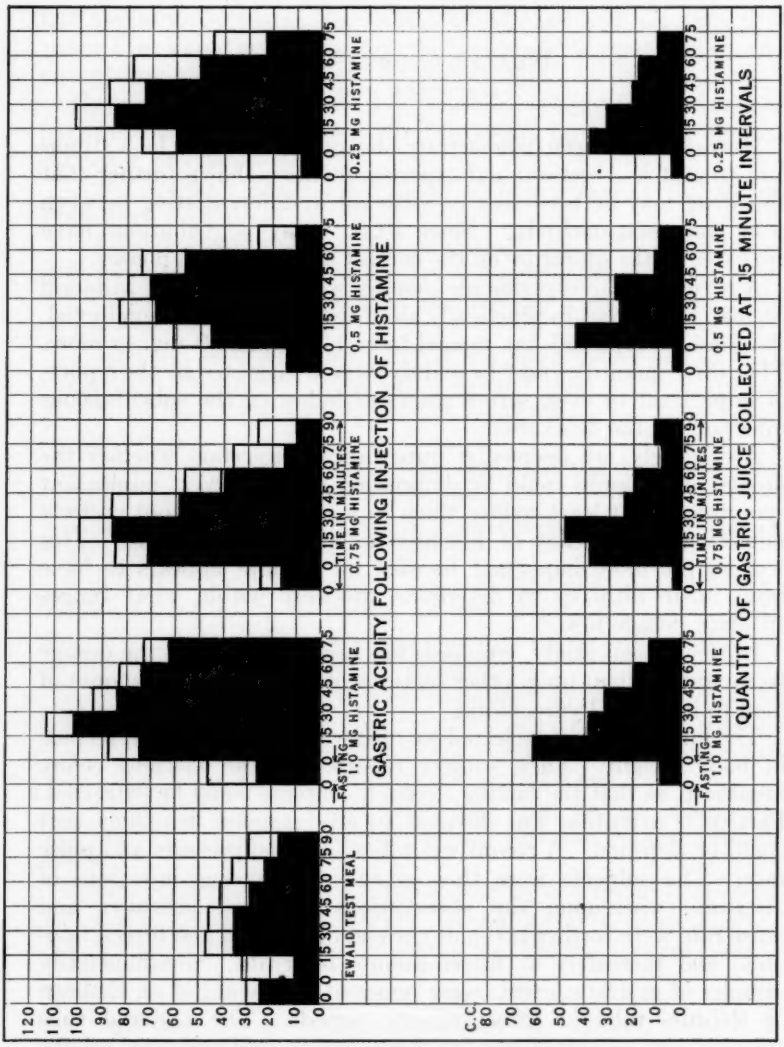

CHART I.—Gastric response to subcutaneous injections of histamin. Subject A.

was done to compare gastric secretion on the same individual when no drug was given.

The preparation of histamin employed was the commercial Imido-Roche 1 cc. (1:1000) = 1 mg. introduced in dosages of 1 mg.,

0.75 mg., 0.50 mg., and 0.25 mg., respectively. Following the 1-mg. dose, and within five minutes after injection there developed a marked erythema of the face, neck and upper part of the thorax

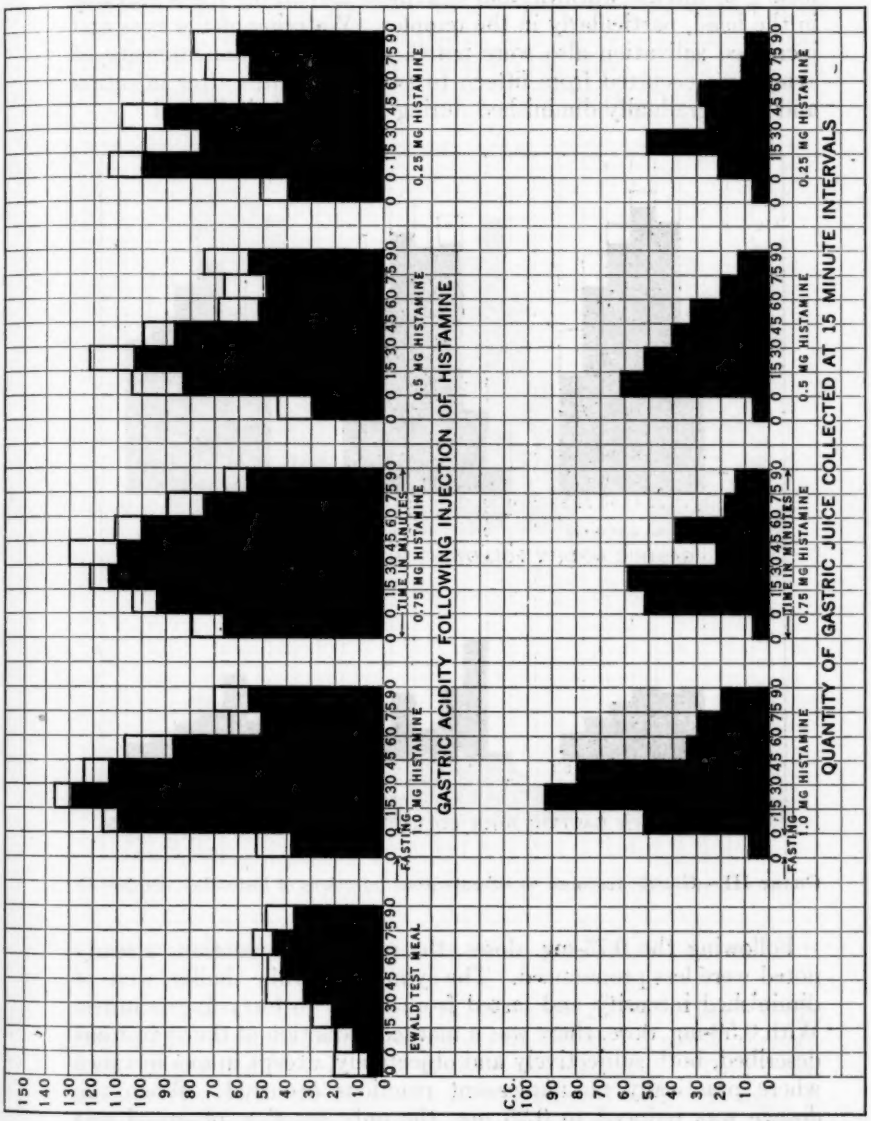

CHART II.—Gastric response to subcutaneous injections of histamin. Subject B.

which persisted for about forty-five to fifty minutes. Also, at the site of injection, there appeared an elevated white wheal, irregular in outline measuring about 5 cm. in diameter, surrounded by a large

area of erythema and accompanied by an itching and stinging sensation. This local reaction at the site lasted about forty-five to sixty minutes and in every instance there was a flushing of the face, a feeling of intense warmth, and heaviness and throbbing sensations in the head, particularly in the temples. Watering of the eyes and increased salivation also were noted. The maximum intensity of symptoms occurred from fifteen to twenty minutes after injection and then gradually diminished during the periods indicated.

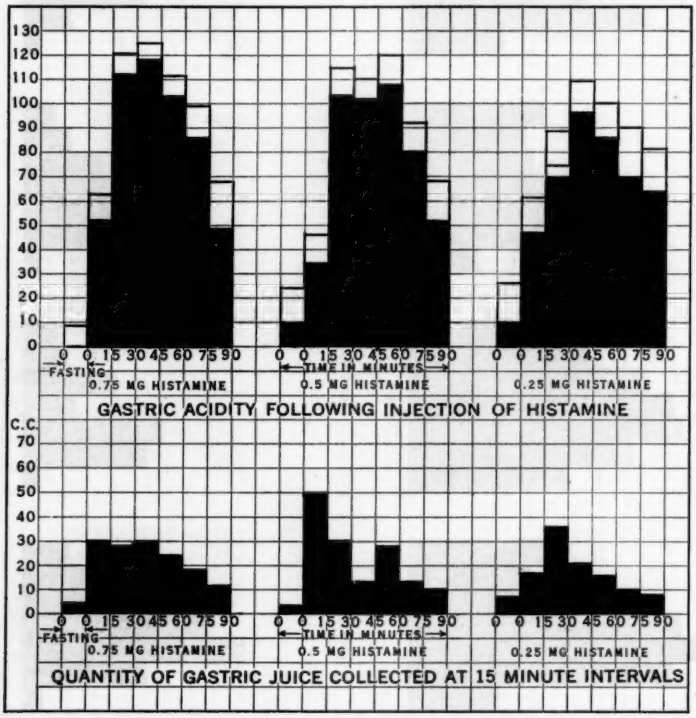

CHART III.—Gastric response to subcutaneous injections of histamin. Subject C.

Following the 0.75-mg. doses, the unpleasant reactions already noted were less pronounced. The symptoms, while similar, were of diminished intensity and lasted from thirty to forty-five minutes. With 0.50-mg. dose, there was a marked reduction of the symptoms described, both subjectively and objectively, except in one instance where practically no unpleasant reactions occurred. When the dosage was reduced to 0.25 mg. the only reaction observed was the appearance of a small wheal at the sight of injection, which was of very short duration and in some subjects a faint flushing of the face without any subjective feeling of warmth.

None of the four dosages just mentioned gave rise to any appreciable difference in the pulse rate or blood pressure, except that in some instances the former increased at most 10 beats while the blood pressure fell about 10 mm. (see table). Even with the smaller doses referred to, histamin remains potent as a gastric stimulant in confirmation of our earlier observations on the effect of this drug. In every instance, there was promotion of gastric secretion and acidity

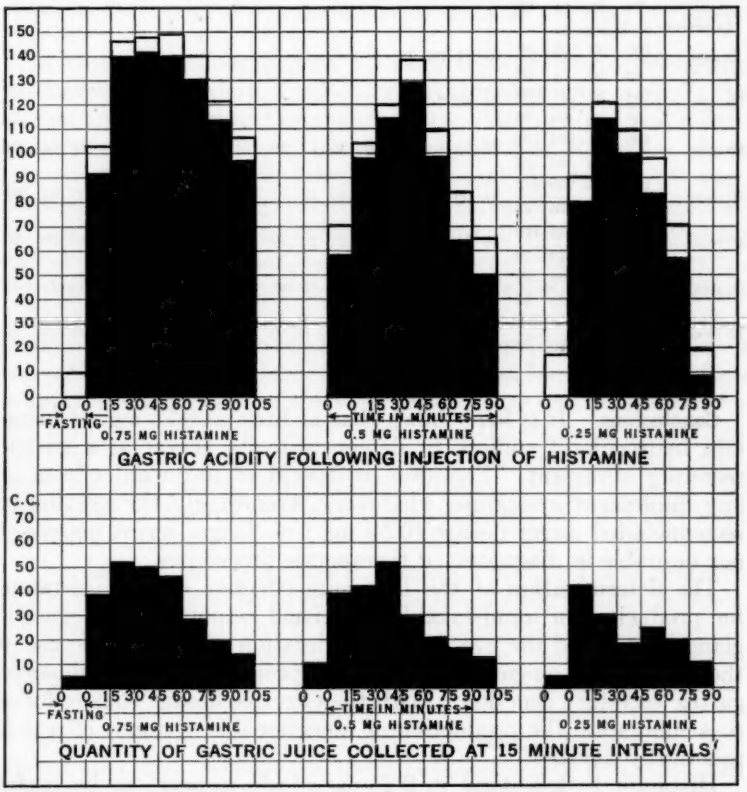

CHART IV.—Gastric response to subcutaneous injections of histamin. Subject D.

within a period of thirty to forty-five minutes after injection. While larger doses produce greater responses, the results are not mathematically proportional to the sizes of the doses employed. Thus 1 mg. does not produce four times the effect observed with 0.25 mg. It should also be noted that the secretion and acidity resulting from the 0.25-mg. injection is considerably greater than that following a standard test meal. This is well illustrated in Charts I and II.

THE SYSTEMIC EFFECTS AND GASTRIC SECRETORY RESPONSE PRODUCED IN THE SAME INDIVIDUAL BY DIFFERENT DOSES OF HISTAMIN.

Time.	Blood pressure. mg. 1	.75	.50	.25	Pulse rate. mg. 1	.75	.50	.25	Vol. secretion. mg. 1	.75	.50	.25	Free HCl. mg. 1	.75	.50	.25	Total acidity. mg. 1	.75	.50	.25
									c.c.											
Fasting	110	100	112	100	68	72	64	72	20	4	8	30	24	14	0	6	40	24	14	30
	76	74	66	60																
Injection	of Histamin																			
5 min.	106	90	110	90	70	82	68	72												
	62	60	74	60																
10 min.	104	90	108	100	76	82	70	60												
	60	60	60	70																
15 min.	100	94	104	100	76	66	64	68	60	35	12	38	74	70	44	60	86	84	62	74
	60	60	66	64																
30 min.	100	96	106	102	64	66	66	68	35	45	23	32	102	86	68	84	114	100	82	102
	66	66	70	66																
45 min.	104	94	108	100	70	64	66	68	12	22	25	20	84	74	70	72	94	86	80	86
	74	68	72	70																
60 min.	106	100	108	98	70	64	64	70	12	18	10	18	74	40	54	52	84	36	74	78
	76	70	80	68																
75 min.	108	100	110	100	70	64	64	66	8	10	8	10	62	14	8	22	74	28	26	44
	78	74	76	72																

Conclusions. It is here shown that as little as 0.25 mg. of histamin hydrochlorid suffices to demonstrate its action as a gastric secretory stimulant. This dose is devoid of untoward effects or any unpleasant symptoms whatever. Accordingly the previously recommended larger dosage (0.50 mg.) no longer seems necessary nor desirable in diagnostic or therapeutic procedures.

The determination of the minimum effective dose of histamin for producing an unmistakable functional response of the gastric glands has paved the way for a consideration of the possible use of the drug for therapeutic purposes in appropriate cases of impaired gastric secretory function. With the effective dosage thus reduced to a minimum, the production of objectionable systemic effects is practically averted.

Histamin hydrochlorid in 0.25-mg. doses appears to be useful in all conditions where a safe and efficient gastric stimulant is indicated.

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OBSERVATIONS ON PEPTIC ULCER. VI. PRELIMINARY REPORT OF CLINICAL EXPERIMENTS WITH GASTRO-DUODENAL ANALYSIS.

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In several previous papers[2-6] I have reported the experimental production and healing of subacute and chronic peptic ulcers in the stomach, duodenum and jejunum of dogs. Both grossly and microscopically these ulcers were indistinguishable from the peptic ulcers encountered clinically in the stomach and duodenum of man. Furthermore, they always occurred in the same locations in the stomach and intestine of the experimental animal that most frequently harbor peptic ulcer in man, namely, the lesser curvature of the stomach and the first portion of the duodenum just distal to the pylorus.

An analysis of the factors involved in the experiments on dogs demonstrated that the formation of typical peptic ulcers followed the withdrawal of alkali from the stomach and intestine into which it emptied and the site of the ulcer in each case was determined by the point at which the forces exerted by the stomach in ejecting the acid chyme converged. Healing of the ulcers ensued when measures were taken to reintroduce alkali into the region of the ulcer or when the forces of the acid ejections of the stomach were diffused or counteracted.

The data of the experiments suggested the probable presence in the normal dog of some relative balance at the pylorus between the acidity of the stomach and the alkalinity of the duodenum. Because of the close similarity in every respect between the experimentally produced peptic ulcers and the peptic ulcers encountered in man, I conceived the following series of experiments on groups of patients free from peptic ulcer and those having peptic ulcer. For convenience, the technique of the experiments to be described was given the name "gastroduodenal analysis."

While the series is not large, the constancy of the results in each group seemed to justify this communication which is presented as a preliminary report.

Methods of Experimentation. The simplest means of determining the relative concentrations of acid and alkali in the stomach and duodenum seemed to be by the passage of tubes into the stomach and duodenum respectively and the withdrawal of samples of their contents for titration.

The technique employed was as follows: As in ordinary gastric analyses, no food was given the patient during the night preceding

the morning of the test. With the patient in the sitting posture a soft graduated, Rehfuss tube was passed into the stomach, this point being indicated by the first mark on the tube. The patient was then made to lie on the right side and the tube was passed farther until the second mark was almost reached. About twenty minutes was then consumed in passing the tube as far as the third mark which indicates the length of the tube necessary to lodge the metal tip in the duodenum. In some cases the passage of the tube through the pylorus seemed to be facilitated by allowing the patient a swallow of water at the time the metal tip was in the region of the pylorus.

After the duodenal tube had been passed the patient was allowed to eat the usual Ewald test meal consisting of two slices of bread without the crust and a glass of water. In order to make sure that the end of the tube remained in the duodenum the patient was kept lying on the right side for the entire period of the test.

For the withdrawal of material from the stomach, a second Rehfuss tube was passed into the stomach. In this way samples of their contents could be withdrawn from both the stomach and the duodenum simultaneously at any time after the ingestion of the test meal. For the withdrawal of samples ordinary glass syringes of 25-cc. to 50-cc. capacity were used.

In order to have accurate information as to the exact position of the tubes in the stomach and duodenum, fluoroscopic examinations were made during the course of every experiment. In all cases, the tubes and their metal tips were well depicted by the Roentgen rays. In some experiments, roentgenograms were made (Fig. 1).

Samples withdrawn from the stomach and duodenum were carefully labeled as to their source and the time of their withdrawal. They were titrated within a few minutes after their withdrawal.

The simplest method of titration proved to be the same as that usually employed in the ordinary examination of contents from the stomach. The material to be tested was measured and a tenth normal solution of sodium hydroxide (NaOH) used for titration. Dimethyl-amino-azo-benzol and phenolphthalein were used as indicators for the free hydrochloric acid (HCl) and the total acids respectively. The results were expressed in terms of "acidity per cent," the method commonly employed for recording gastric acidity.

Results. *General Observations.* In most cases the patients did not object to the passage of two Rehfuss tubes. In some experiments the tubes were left in place for as much as two hours without discomfort.

The passage of a tube into the duodenum was usually evidenced by the character of the material which could be withdrawn from the tube in small amounts. This was a yellow fluid which seemed to contain large quantities of bile. It contrasted sharply with the cloudy, white material characteristic of the contents of the stomach.

In some experiments in which the tube for passage into the duodenum did not pass the pylorus in the usual way, the Ewald test

FIG. 1.—The metal tip of the first tube is in the duodenum just beyond the pylorus The metal tip of the second tube is in the upper part of the stomach.

meal was given with the patient lying on the right side and as the digested portions of the meal entered the duodenum the tip of the Rehfuss tube accompanied them.

Chyme could be withdrawn from the stomach in an almost continuous stream, the total amount being determined only by the total volume of chyme in the stomach. Material from the duodenum, however, could be withdrawn only in small amounts at one time and seemed to come in periodic spurts as though representing cyclic ejections of chyme from the stomach.

In some instances, the fluoroscopic examination revealed the tip of the duodenal tube lodged in the stomach just on the gastric side of the pylorus. Material withdrawn from tubes in this location was very similar in appearance to that usually obtained from the duodenum. The acidity of such samples was higher than that of the contents of the duodenum but lower than that of the gastric chyme.

Observations on Persons without Peptic Ulcer. For the experiments of this group, two types of patients were selected: For the first, those who had no complaints, symptoms or signs referable to the abdomen or gastrointestinal tract (Table I), for the second, those who complained of pains in the abdomen but who did not have any symptoms or signs of peptic ulcer (Table II).

Gastroduodenal analyses were made satisfactorily in 13 persons who did not have a peptic ulcer. Of this number 5 were normal except for slight wounds of the extremities. Of the remaining 8, 3 had gastric neuroses, 1 had chronic appendicitis, 2 had cholecystic disease, 1 had gastric achlorhydria, and 1 had pyloric achalasia, a spasmodic narrowing of the pylorus with inability to relax properly. In all of the patients the first tube passed into the duodenum with relative ease except in the case of the patient with pyloric achalasia in whom several attempts were made on successive days before the tube finally passed the pylorus.

Examination of the contents of the stomach in these 13 persons showed a wide variation in the concentrations of the free hydrochloric acid and the total acids. This was true in both the normal patients and those with abdominal symptoms from diseases other than peptic ulcer. In spite of this wide variation in the acidity in the stomach the acidity of the duodenal contents was always low and relatively constant.

Of this group of 13 patients that did not have peptic ulcer the most constant feature was the complete absence of free hydrochloric acid in the material withdrawn from the duodenum. The only exception in the group was in the case with pyloric achalasia.

Observations on Persons with Peptic Ulcer. Gastroduodenal analyses were attempted in 23 patients with peptic ulcer. It was impossible to get a duodenal tube past the pylorus in more than 8 of this number, although two or more attempts were sometimes made.

TABLE I.—GASTRIC AND DUODENAL ACIDITY. NORMAL PATIENTS. NO ABDOMINAL COMPLAINT.

Patient.	Age.	Diagnosis.	Titration in "acidity per cent."				Time interval between test meal and its withdrawal.	Remarks.
			Stomach		Duodenum.			
			Free HCl.	Total acids.	Free HCl.	Total acids.		
Miss L. S.	16	Laceration, hand	...	....	0°	7°	¼ hr.	
			...	....	0°	20°	½ hr.	
			10°	25°	0°	6°	1 hr.	
Mr. R. S.	21	Burn, knee	33°	68°	0°	8°	1 hr.	
Mr. T. T.	19	Wound, knee	18°	28°	0°	10°	1 hr.	
Mr. L. C.	18	Laceration, foot	35°	135°	0°	18°	1 hr.	
Mr. M. J.	19	Wound, leg	28°	64°	0°	35°	1 hr.	

TABLE II.—PATIENTS WITH ABDOMINAL COMPLAINTS BUT WITHOUT PEPTIC ULFER.

Patient.	Age.	Diagnosis.	Titration in "acidity per cent."				Time interval between test meal and its withdrawal.	Remarks.
			Stomach		Duodenum.			
			Free HCl.	Total acids.	Free HCl.	Total acids.		
Mr. J. S.	21	Gastric neurosis	50°	70°	0°	10°	1 hr.	Roentgenologic examination of stomach, etc., negative.
Mr. M. H.	67	Gastric neurosis	58°	66°	0°	15°	1 hr.	Roentgenologic examination of stomach, etc., negative.
Mr. R. B. B.	23	Gastric neurosis	32°	44°	0°	12°	1 hr.	Roentgenologic examination of stomach, etc., negative.
			...	....	0°	6°	1¼ hrs.	
Mr. E. J.	47	Chronic appendicitis	44°	74°	0°	10°	1 hr.	Roentgenologic examination of stomach, etc., negative.
Mrs. C. M.	36	Chronic cholecystitis	15°	30°	0°	12°	1 hr.	Diagnosis verified at operation.
Mr. R. B.	53	Solitary cholelithiasis	40°	60°	0°	20°	1 hr.	Roentgenologic diagnosis.
Mr. E. L.	70	Achlorhydria gastrica	0°	15°	0°	10°	1 hr.	Roentgenologic and laboratory diagnosis. Exploratory laparotomy refused.
Mr. C. T.	42	Pyloric achalasia	30°	55°	14°	25°	1 hr.	Roentgenologic diagnosis, verified at operation.

Mr. L. P.	46	Hemorrhagic gastritis						laparotomy refused.
Mr. C. T.	42	Pyloric achalasia	30°	55°	14°	25°	1 hr.	Roentgenologic diagnosis, verified at operation.

TABLE III.—PATIENTS WITH PEPTIC ULCER.

Patient.	Age.	Diagnosis.	Titration in "acidity per cent."				Time interval between test meal and its withdrawal.	Remarks.
			Stomach		Duodenum.			
			Free HCl.	Total acids.	Free HCl.	Total acids.		
Dr. M. W.	25	Duodenal ulcer	44°	56°	14°	30°	1 hr.	Clinical and roentgenologic diagnosis.
Mr. G. P.	39	Duodenal ulcer	43°	52°	13°	22°	1 hr.	Clinical and roentgenologic diagnosis.
Mr. L. S.	31	Duodenal ulcer	57°	77°	...	...	½ hr.	Clinical and roentgenologic diagnosis.
			42°	53°	...	...	1 hr.	
			...	....	9°	17°	1¼ hr.	
Mrs. B. B.	26	Duodenal ulcer	33°	52°	10°	40°	1 hr.	Clinical and roentgenologic diagnosis.
			...	....	20°	47°		
			...	....	13°	36°		
			29°	46°	5°	16°	1¼ hrs.	
Miss R. P.	52	Duodenal ulcer	84°	92°	26°	36°	1 hr.	Clinical and roentgenologic diagnosis.
Dr. J. K.	..	Duodenal ulcer	7°	17°	2°	14°	1 hr.	Clinical and roentgenologic diagnosis.
			5°	20°	0°	18°		
Mrs. P. G.	67	Gastric ulcer; cancer?	2°	4°	0°	0°	1 hr.	Clinical and roentgenologic diagnosis. Exploratory laparotomy refused.
Mrs. P. W.	32	Gastric ulcer	15°	24°	3°	20°	1 hr.	Clinical and roentgenologic diagnosis. Exploratory laparotomy refused.

Of the 8 patients in whom gastroduodenal analysis was accomplished, 6 had ulcer of the duodenum and 2 had ulcer of the stomach (Table III). As in the preceding group of patients, the acidity of the contents of the stomach varied widely. The acidity of the duodenal contents showed wider variations and was in general higher than in the patients who did not have peptic ulcer.

The most constant feature of this group of 8 patients with peptic ulcer was that all except 1 showed the presence of free hydrochloric acid in the samples of duodenal contents. In this case, the gastric acidity was very low.

Discussion. Both the experimental and clinical data on peptic ulcer seem to suggest that the site of ulceration is determined by mechanical factors. The trauma administered to the mucosa by the propelling of food along the lesser curvature and the ejection of food from the nozzle-like pylorus against the wall of the duodenum offers a plausible explanation for the usual occurrence of peptic ulcer in these locations.

The data of previously reported experiments on dogs suggested that the chronicity of peptic ulcer might be due to a relative imbalance between the acids of the stomach and the alkalies of the duodenum with a resulting preponderance of the acid.

Many workers have linked gastric hyperacidity with peptic ulcer but so many cases of hyperacidity were found without peptic ulcer and so many cases of peptic ulcer occurred without hyperacidity that the usual type of gastric analysis offered little or no aid in studying the etiology of peptic ulcer or in diagnosing the disease. This fact is illustrated by the wide variations in the gastric acidity of the patients in these experiments.

It is generally believed that the alkalies of the duodenum, the bile, pancreatic juice, and duodenal secretion, neutralize the acids of the stomach during digestion. Partial neutralization takes place in the pyloric portion of the stomach by regurgitation of secretions from the duodenum and neutralization is completed after the gastric chyme enters the duodenum.

The experiments on patients without peptic ulcer seem to substantiate this belief. Regardless of the variation in the concentration of acid in the stomach neutralization occurred in the duodenum and samples of material withdrawn from the duodenum showed no free hydrochloric acid and only a small but fairly constant concentration of total acids. After the completion of these experiments a reference was found to the work of Baird, Campbell and Hearn.[1] In experiments of a somewhat similar nature, they investigated the acidity of the duodenum in normal persons only. They obtained results similar to my own in normal persons. They did not investigate any patients with peptic ulcer.

In my experiments the absence of free hydrochloric acid in the duodenum occurred only in those patients who did not have peptic

ulcer. In those who did have peptic ulcer neutralization was not complete and samples of material withdrawn from the duodenum showed the presence of free hydrochloric acid and a considerable range of variation in the concentration of total acids.

The experiments suggest, therefore, the presence of a relative acid-alkali balance between the secretions of the stomach and duodenum in normal individuals and a relative acid-alkali imbalance in those persons with peptic ulcer.

Such an imbalance might be produced in several ways: by a hypersecretion of acid, by a hyposecretion of alkali, by a combination of the two, or by improper functioning of the pylorus, thereby preventing the normal interchange between the contents of the stomach and duodenum. The importance of the last factor is suggested by the difficulty encountered in passing a tube through the pylorus in the experiments on all persons with peptic ulcer and by the atypical findings in the experiment in which pyloric achalasia was present.

Provided the data of these experiments can be verified in a larger series of cases it seems probable that they may help to clarify the problem of the etiology of peptic ulcer. The site of ulceration may be attributable to mechanical factors and the chronicity of the ulcer to insufficient or improper neutralization of the acid gastric chyme caused by altered physiologic processes. Furthermore gastroduodenal analysis may find some application as a measure to assist in the diagnosis of peptic ulcer.

Summary. Some of the author's previously reported experiments with the production and healing of peptic ulcers in dogs are briefly reviewed. The experiments suggested the importance of mechanical and chemical factors in determining the location and chronicity of the peptic ulcers.

In a preliminary report some experiments are described in which tubes were passed into the stomach and duodenum in two groups of patients: those without peptic ulcer and those with peptic ulcer. The position of all tubes was verified roentgenologically. Ewald test meals were eaten by the patients and afterward samples of material were withdrawn from the stomach and duodenum simultaneously.

In persons without peptic ulcer, no free hydrochloric acid was recovered in samples of the contents of the duodenum. In persons with peptic ulcer, free hydrochloric acid was found in samples from the duodenum. The experiments on patients suggested the presence of a relative acid-alkali balance between the secretions of the stomach and duodenum in normal persons and a relative acid-alkali imbalance in those persons with peptic ulcer.

An analysis of the factors involved in these and previous experiments suggested the probability that the site of peptic ulcer is determined by mechanical factors and that the chronicity may be due to a relative imbalance between the acids of the stomach and

the alkalies of the duodenum, causing incomplete or faulty neutralization of the acid gastric chyme. Improper functioning of the pylorus may be an important factor in causing the acid-alkali imbalance.

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THE EXTENT OF THE VARIATIONS IN THE LEUKOCYTES OF NORMAL INDIVIDUALS.

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The value of the leukocytic formula in any pathologic condition depends very largely upon its variation from the normal. To evaluate any pathologic formula when followed over a considerable period of time it would appear necessary to establish the variation of the leukocytes in normal individuals over a relative period. From a survey of the literature it seems that but little work has been done on this particular phase in studies of the leukocytes. The reports made have been on a few individuals studied under especial conditions and have been made very largely on the male sex.

For the past two years the leukocytic reactions in tuberculous cases of both sexes have been followed by weekly counts taken at relatively the same time of day and on the same day of the week. To establish a normal as a basis for comparison of these studies a group of 17 average normal individuals was followed for a period of eleven weeks. The present report gives the data obtained from the blood counts on the normal group.

The group studied consisted of 9 adult males and 8 adult females. The age range in the male was from eighteen to forty years, and in the female from twenty-four to fifty-two years. Every case was examined physically and roentgenograms of the chest were made

to rule out any evidence of active pulmonary disease. It is almost impossible to get a sufficient number of perfectly normal chests, by Roentgen ray, for study, so that this group contains what may be called the average "normal" chest. The group proved to be in good health, as but two counts were missed on account of disabling illness—both acute upper respiratory infections.

The main point in the problem was to get the extent of the leukocytic variation among a group of healthy people pursuing their usual mode of life. It was desired to get the greatest variation normal individuals might show. It was felt that people residing in a large city lived a more strenuous life than those residing in a rural setting, consequently New York City was chosen as the place where normal individuals would lead the most hectic existence. Physicians and nurses always lead a life of great irregularity and are more constantly in contact with individuals suffering from all types of infection than any other group of normal individuals, therefore the individuals taken for this study were all from the medical division at the Home Office of the Metropolitan Life Insurance Company. Statistics show that there occurs a larger number of acute infections, respiratory infections in particular, in New York City in January, February and March than at any other time of the year, so that this period of the year was deliberately chosen to carry on the study. In brief, the conditions under which the study was made were such that one would expect to get the greatest variation that was consistent with health. It is of course recognized that similar studies of normal individuals in a different environment might easily give considerably different averages and extremes.

Method. All of the total and differential counts and the obtaining of the blood samples were done by the author. The morning samples were obtained between 9.30 and 10.15, except where noted to the contrary, and the afternoon samples were obtained between 2.30 and 3.15. Two individuals had afternoon counts throughout the study. In 11 the examinations were all made in the morning, and in 4 cases morning examinations were made the first six weeks and afternoon examinations thereafter. Weekly counts, on Friday of each week, were done for ten weeks. For the last week of the study daily counts were made for five days. In all, 241 counts out of a possible 247, were done. In each individual a careful record was kept of "head colds" and any other minor ailment, and in the females a careful record of the menses, without the knowledge of the author until the study had been completed.

The following technique has been used in all counts. It has been found to give consistent results and is as simple as possible when one desires a fair degree of accuracy. Another method may give greater accuracy but it is felt that the value of any technique lies in the rigid adherence to a routine procedure when it has been found to give consistent results.

All diluting pipettes and double Levy counting chambers used in this study have been certified by the United States Bureau of Standards. The same pipettes and counting chambers have been used in the counting of over 4000 samples of blood and have been found to be accurate within small variations.

The blood for the total counts has all been diluted twenty times. The pipettes have been vigorously shaken two minutes at the time the blood was taken, and three minutes more before being placed in the counting chamber. Two samples from the pipettes were placed in the double counting chamber. At least 2 drops of the diluted blood was discarded between the two samples. Two large squares, diagonally opposite, were counted in each chamber and the average of the four squares was taken for the total count.

The blood smears were made on cover glasses. The cover glasses were moved across the drop of blood to be examined so that a line of blood 1 to 2 mm. wide was obtained. In this way the blood spreads in a straight line, not in a circle.

All smears have been stained with Wright's blood stain. In all differentials 400 cells have been counted. The high dry objective and a No. 10 ocular have been used instead of a higher magnification.

No attempt has been made to classify the lymphocytes into groups of the large and small type. All cells which had a finely granular, muddy blue cytoplasm have been classed as large mononuclear leukocytes, regardless of the shape of the nucleus. The nucleus in this cell may be round, oval, bean-shaped, horse-shoe shaped, or considerably lobulated. The usual grouping of the granulocytic series has been followed.

Results. The following is the record of the counts and other data on each of the individuals:

GROUP I.—LEUKOCYTE AND DIFFERENTIAL COUNTS—(ALL COUNTS BETWEEN 9.30 AND 10.15 A.M.).*

1. Dr. E., female, aged twenty-eight years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	8100	58.0	4700	32.0	2600	8.0	650	1.5	120	0.5	40	
1–13	6800	46.0	3100	40.0	2700	8.0	540	5.0	340	1.0	70	
1–20	6800	49.0	3300	34.0	2300	11.0	750	5.0	340	1.0	70	
1–27	5400	48.0	2600	39.0	2100	9.0	490	3.0	160	1.5	80	Menses.
2–3	6400	48.0	3100	35.0	2200	11.0	700	4.5	290	1.5	100	
2–10	5400	48.0	2600	28.0	2000	8.0	430	3.0	160	2.0	90	Coryza.
2–17	6700	47.0	3100	36.0	2400	11.0	740	4.0	270	2.0	130	
2–24	5200	47.0	2400	35.0	1800	9.0	470	8.0	420	1.0	50	Menses.
3–2	5200	38.0	2000	44.0	2300	11.0	570	6.0	310	1.0	50	
3–9	Absent	—sinus infection		...	...	...	...	...	...	...	...	Still considerable discharge from sinus.
3–15	9100	54.0	4900	30.0	2700	10.5	950	5.0	450	0.5	40	
3–16	6500	67.0	4400	21.0	1400	6.0	390	5.0	320	1.0	60	
3–19	7300	56.0	4100	29.0	2100	10.5	770	3.5	250	1.0	70	Menses.
3–20	8000	49.0	3900	35.0	2800	11.0	880	4.5	360	0.5	40	Menses.

* The total cells in all of the charts are accurate to within 100 cells for the neutrophils and lymphocytes and within 10 cells for the other cell types.

2. Dr. H., male, aged thirty-eight years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	5,400	47.0	2500	40.0	2100	9.0	480	4.0	220	0		
1–13	6,300	55.0	3500	32.0	2000	10.0	630	2.0	130	1.0	60	
1–20	6,000	55.0	3300	33.0	2000	11.0	660	1.0	60	0		
1–27	10,200	55.0	5600	33.0	3400	10.0	1020	2.0	200	0	..	Coryza.
2–3	8,000	45.5	3600	40.0	3200	12.0	960	1.5	120	1.0	80	
2–10	7,400	56.0	4100	34.0	2500	8.0	590	1.5	110	0.5	40	
2–17	5,400	55.0	3000	32.0	1700	10.0	540	2.5	130	0.5	30	Coryza.
2–24	5,600	46.5	2600	41.0	2300	10.0	560	2.0	110	0.5	30	
3–2	6,100	52.0	3200	36.0	2200	9.5	580	2.0	120	0.5	30	Bad tracheitis for 2 days.
3–9	9,200	64.0	5900	23.0	2100	10.5	870	2.5	230	0	..	Coryza.
3–15	5,200	54.0	2800	34.0	1800	8.5	440	3.0	110	0.5	30	
3–16	5,900	52.0	3100	38.0	2200	8.0	470	2.0	120	0		
3–19	6,300	50.0	3200	37.0	2300	10.0	630	2.0	130	1.0	60	
3–20	6,900	48.0	3300	41.0	2800	8.0	550	2.5	140	0.5	30	Coryza.

3. Mr. R., aged thirty-eight years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	7,000	50.0	3500	39.0	2800	9.0	640	1.0	70	0		
1–13	8,500	56.0	4700	35.5	3000	7.0	600	1.0	80	0.5	40	
1–20	10,800	58.5	6300	31.0	3300	9.0	970	0.5	50	0	..	Extra heavy work and long hours in preparation for annual convention.
1–27	11,800	49.0	5800	41.0	4800	9.0	1060	0.5	60	0.5	60	
2–3	9,400	59.0	5500	34.0	3200	6.0	560	0.5	50	0.5	50	
2–10	8,900	56.0	5000	34.0	3000	9.0	800	1.0	90	0		
2–17	9,000	56.0	5000	35.0	3100	8.0	720	0.5	40	0.5	40	
2–24	5,400	51.0	2700	39.0	2100	9.0	480	1.0	50	0		
3–2	8,200	58.0	4700	31.0	2500	10.0	820	1.0	80	0		
3–9	7,400	55.0	4000	33.0	2400	9.0	660	2.5	180	0.5	40	
3–15	6,200	44.0	2700	45.0	2800	9.0	560	1.0	60	1.0	60	
3–16	7,100	47.0	3300	43.0	3000	8.5	600	1.0	70	0.5	30	
3–17	6,600	41.0	2700	45.0	3000	12.0	790	1.5	100	0.5	30	
3–18	7,300	45.5	3300	44.0	3200	10.0	730	0.5	40	0		
3–20	6,600	55.0	3600	36.0	2400	5.5	360	3.0	190	0.5	30	

4. Mrs. S., aged thirty-one years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	7300	52.0	3800	37.0	2700	10.0	730	0.5	40	0.5	40	
1–13	7100	54.0	3800	33.0	2400	9.0	640	3.0	210	0		
1–20	8600	59.0	5100	29.0	2500	9.0	780	1.5	130	1.5	130	
1–27	8600	57.0	4900	31.0	2600	10.0	860	1.5	130	0.5	40	
2–3	8200	68.0	5600	24.0	2000	6.0	490	1.5	120	0.5	40	Menses; coryza and laryngitis for 3 days.
2–10	6300	59.0	3700	31.0	2000	7.0	440	2.0	130	1.0	60	
2–17	6900	53.5	3200	36.0	2100	8.0	470	2.0	120	0.5	30	
2–24	8100	61.0	4900	30.0	2400	7.5	610	1.0	80	0.5	40	
3–2	6200	59.0	3700	27.0	1700	11.0	680	2.0	120	1.0	60	
3–9	6200	56.0	3500	35.0	2200	8.0	500	1.0	60	0		
3–15	6300	58.0	3700	33.0	2100	7.0	440	1.0	60	1.0	60	
3–16	6000	58.0	3500	32.0	1900	8.0	480	1.0	60	1.0	60	
3–17	7300	60.0	4400	32.0	2300	6.5	480	1.0	70	0.5	40	
3–19	9500	61.5	5800	30.0	2800	7.0	660	1.0	90	0.5	50	Tired.
3–20	6700	62.0	4200	30.0	2000	6.5	440	1.0	70	0.5	40	

5. Dr. B., male, aged thirty-three years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	8,700	66.0	5700	25.0	2200	8.0	700	1.0	90	0		
1-13	10,000	52.0	5200	38.0	3800	8.0	800	1.5	150	0.5	50	
1-20	8,800	61.5	5400	27.0	2400	9.0	790	2.0	180	0.5	40	
1-27	8,500	58.0	4900	31.0	2700	9.0	770	2.5	220	0.5	40	Coryza for 2 days.
2-3	8,900	65.0	5700	24.5	2300	9.0	800	1.0	90	0.5	40	Coryza.
2-10	9,600	63.0	6000	22.5	2200	12.0	1150	2.0	190	0.5	50	
2-17	8,200	62.0	5100	28.0	2300	8.0	660	1.5	120	0.5	40	
2-24	9,700	60.0	5800	32.0	3100	6.0	580	2.0	190	0		
3-2	7,600	54.0	4100	35.0	2700	9.0	680	2.0	150	0		
3-9	7,200	60.0	4300	32.0	2300	6.0	430	2.0	140	0	..	Count taken at 11.15 A.M.
3-15	9,700	56.0	5400	30.0	2900	9.5	920	4.0	390	0.5	50	
3-16	8,500	61.0	5200	29.0	2400	9.0	760	1.0	80	0		
3-17	7,200	61.5	4400	28.0	2000	8.0	570	2.0	140	0.5	40	Mild "grippe."
3-19	7,400	59.0	4400	31.0	2300	5.5	410	3.5	260	1.0	70	Up all night on obstetric case; tired.
3-20	11,000	63.0	6900	25.5	2800	9.0	990	2.0	220	0.5	60	

6. Dr. B., female, aged fifty-two years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	8,000	55.0	4400	35.0	2800	7.0	560	2.0	160	0.5	40	
1-20	6,600	55.5	3700	35.0	2300	8.0	530	1.0	70	0.5	30	Coryza.
1-27	9,000	58.0	5200	32.0	2900	7.0	630	1.5	130	0.5	40	
2-10	11,800	67.0	7900	24.0	2800	6.0	710	3.0	350	0	..	Not fully recovered from attack of "grippe."
2-17	9,300	61.0	5700	27.0	2500	7.0	650	4.0	370	1.0	90	
2-24	8,700	56.5	4900	35.0	3000	6.0	520	2.0	170	0.5	40	
3-2	8,100	54.0	4400	38.0	3100	5.0	410	2.5	200	0.5	40	
3-9	8,900	58.0	5200	34.0	3000	4.0	350	3.0	260	1.0	90	
3-15	9,000	58.5	5300	34.0	3000	4.0	360	3.0	270	0.5	40	
3-16	8,400	56.0	4700	37.0	3100	4.5	380	2.0	170	0.5	40	
3-17	9,200	59.0	5400	32.0	2900	6.0	550	2.5	230	0.5	40	
3-19	9,000	60.0	5400	28.0	2600	6.0	540	4.5	410	1.5	130	Mild indigestion.
3-20	10,900	62.5	6800	31.0	3400	6.0	650	0.5	50	0	..	Mild indigestion.

7. Dr. S., male, aged thirty years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7,300	49.0	3,600	42.0	3000	7.0	510	1.5	110	0.5	40	
1-20	7,800	57.0	4,400	29.0	2200	12.5	980	1.5	130	0	..	Abscessed tooth removed yesterday; face swollen.
1-27	5,600	50.0	2,800	42.0	2300	7.0	390	0.5	30	0.5	30	
2-3	9,400	70.0	6,500	24.0	2200	5.0	470	1.0	90	0		
2-10	7,800	55.0	4,300	35.5	2800	8.0	620	1.0	80	0.5	40	
2-17	8,700	67.0	5,800	26.0	2200	5.0	430	1.5	130	0.5	40	
2-24	6,500	43.0	2,800	48.0	3100	7.0	450	1.5	100	0.5	30	
3-2	6,200	47.0	2,900	43.0	2600	8.0	490	1.0	60	1.0	60	
3-9	7,200	49.0	3,500	43.0	3100	6.0	430	2.0	140	0		
3-15	6,400	46.0	2,900	45.0	2900	6.0	380	2.0	130	1.0	60	
3-16	9,200	47.0	4,300	40.0	3700	8.0	730	1.5	140	3.5	330	
3-17	7,600	61.0	4,600	29.0	2200	6.0	450	2.0	150	2.0	150	
3-19	6,100	53.0	3,200	36.0	2200	8.5	520	2.0	120	0.5	30	
3-20	14,400	80.0	11,800	14.0	2000	5.0	720	0.5	80	0.5	70	Felt as if he was going to have acute frontal sinusitis yesterday; feels better today.

8. Dr. B., male, aged thirty-five years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7,300	67.0	4,900	24.0	1700	7.0	510	1.5	110	0.5	40	
1-13	8,000	65.5	5,200	26.0	2100	7.0	560	1.5	120	0		
1-20	8,400	67.0	5,700	24.0	2000	7.5	630	1.0	80	0.5	40	
1-27	10,400	66.5	6,900	24.0	2500	7.0	730	2.0	210	0.5	50	
2-3	7,400	66.0	4,900	24.0	1800	8.0	590	1.5	110	0.5	40	
2-10	9,000	69.0	6,200	21.0	1900	8.0	720	2.0	180	0	..	Coryza.
2-17	7,600	60.0	4,600	30.0	2300	7.0	530	2.5	190	0.5	40	Coryza.
2-24	7,500	67.0	5,000	25.5	1900	6.0	450	1.0	70	0.5	40	Count taken at 11.45 A.M.
3-2	8,000	64.0	5,100	25.0	2000	8.0	640	3.0	240	0		
3-9	12,600	82.0	10,400	13.0	1600	5.0	630	0	..	0	..	Bad omelette for supper; some cramps; 3 loose bowel movements; felt O. K. when count was taken.
3-15	8,500	58.0	4,900	29.0	2400	11.0	930	1.0	80	1.0	80	
3-16	12,000	69.0	8,300	21.0	2500	7.0	840	3.0	360	0	..	But little rest past 24 hrs.; very ill patient.
3-17	7,600	64.0	4,900	27.0	2000	8.0	610	1.0	80	0		
3-19	8,100	71.0	5,700	21.0	1700	6.0	480	2.0	160	0		
3-20	9,800	72.0	7,000	21.0	2000	5.0	490	1.5	150	0.5	50	

9. Mrs. C., aged thirty-eight years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7500	59.0	4400	31.0	2300	8.0	600	1.5	110	0.5	40	
1-13	8000	65.0	5200	27.0	2200	6.0	480	1.0	80	1.0	80	Menses.
1-20	9000	65.0	5800	27.0	2400	6.0	450	1.5	130	0.5	40	
1-27	6000	63.0	3800	27.0	1600	7.0	420	1.5	90	0.5	30	
2-3	7000	61.5	4300	30.0	2100	7.0	490	1.0	70	0.5	30	
2-10	7000	66.0	4600	24.0	1700	8.0	560	1.5	100	0.5	30	Menses.
2-17	6700	62.5	4200	28.0	1900	8.0	540	1.5	100	0		
2-24	7300	66.0	4800	25.0	1800	8.0	580	1.0	70	0		
3-2	9000	61.0	5500	31.0	2800	4.0	360	4.0	360	0	..	Menses; extensive pityriasis developed in last 3 days.
3-9	7800	61.0	4700	27.0	2100	6.0	470	5.5	430	0.5	40	Pityriasis about the same.
3-15	8200	61.0	5000	23.0	1900	12.0	980	3.0	240	1.0	80	Pityriasis much better.
3-16	7000	63.5	4500	24.0	1700	11.0	770	1.5	100	0		
3-17	6600	65.0	4300	24.0	1600	8.0	530	2.5	160	0.5	30	
3-19	8200	62.0	5100	27.0	2200	8.5	700	2.0	160	0.5	40	Menses.
3-20	Absent; vacation.											

10. Mrs. L., aged thirty-six years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7,200	45.0	3200	43.5	3200	8.0	580	3.0	220	0.5	40	
1-13	6,000	46.0	2800	43.0	2600	7.0	420	3.0	180	1.0	60	Menses.
1-20	9,600	66.0	6300	23.0	2200	7.0	670	3.0	290	1.0	100	
1-27	7,400	51.0	3800	38.0	2800	7.0	520	3.0	220	1.0	70	
2-3	10,800	51.0	5400	40.0	4300	6.0	650	2.0	220	1.0	110	Turkish steam bath last night.
2-10	6,600	53.5	3500	36.0	2400	8.0	530	2.0	130	0.5	30	
2-17	8,000	57.0	4600	34.0	2700	6.5	520	2.0	160	0.5	40	
2-24	7,700	48.0	3700	38.0	3000	9.0	690	4.5	340	0.5	40	
3-2	6,700	49.0	3300	42.0	2900	7.0	470	1.0	70	1.0	70	Menses.
3-9	7,800	63.5	5000	29.0	2300	6.0	470	1.5	120	0		
3-15	6,100	44.0	2700	46.0	2800	6.0	360	3.0	180	1.0	60	
3-16	6,700	55.0	3700	35.0	2300	7.0	470	2.0	130	1.0	70	
3-17	8,200	49.0	4000	41.0	3300	7.0	570	2.0	160	1.0	80	
3-19	6,400	52.0	3300	39.0	2500	4.0	260	4.0	250	1.0	60	
3-20	6,600	50.5	3300	39.0	2600	9.0	590	1.5	100	0		

11. Miss H., aged twenty-four years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	11,300	53.0	6000	34.0	3800	12.0	1360	1.0	110	0	..	Menses.
1–13	8,200	49.0	4000	39.0	3200	10.0	820	1.5	120	0.5	40	
1–20	13,100	69.0	7900	29.0	3800	8.0	1050	2.0	260	1.0	130	
1–27	12,300	60.0	6800	32.0	3600	6.0	680	1.5	170	0.5	60	
2–3	7,700	56.0	4300	34.0	2600	8.0	610	2.0	150	0	..	Menses; by request had 2 good nights of rest and quiet at home before count.
2–10	7,700	55.0	4200	36.0	2700	7.0	540	0.5	40	1.5	110	Same routine as requested above.
2–17	11,200	62.5	7000	28.0	3100	8.0	900	1.5	130	0		
2–24	9,000	63.0	5700	25.0	2200	9.0	810	2.0	180	0		
3–2	9,800	55.0	5400	34.0	3300	8.5	830	1.5	150	1.0	100	Menses.
3–9	11,200	52.0	6800	39.0	4400	7.0	780	1.5	170	0.5	60	
3–15	9,200	60.5	5500	31.0	2800	6.0	550	2.0	180	0.5	40	
3–16	12,000	57.0	6800	33.0	3900	9.0	1080	1.0	120	0	..	Feels unusually tired.
3–17	11,000	57.0	6300	35.0	3800	6.0	660	1.5	160	0.5	50	
3–19	10,200	55.0	5600	35.0	3500	8.5	870	1.5	150	0		
3–20	9,800	53.0	5200	36.0	3500	8.5	830	2.0	200	0.5	50	

GROUP II.—(ALL COUNTS BETWEEN 2.30 AND 3.15 P.M.).*

12. Dr. L., male, aged forty years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	8,400	66.0	5500	25.0	2100	7.0	590	1.5	130	0.5	40	
1–13	11,800	69.0	8100	25.0	3000	5.0	590	1.0	120	0		
1–20	8,700	65.0	5700	24.0	2100	8.0	700	3.0	260	0		
1–27	10,300	63.0	6500	29.0	3000	3.5	360	4.0	410	0.5	50	
2–3	8,500	58.0	4900	33.0	2800	6.0	510	2.5	220	0.5	40	
2–10	10,500	66.0	6900	25.0	2600	6.5	680	1.5	160	1.0	100	
2–17	9,600	65.0	6200	26.0	2500	6.0	580	2.5	240	0.5	50	Sore throat early in week.
2–24	8,800	71.0	6200	24.0	2100	4.0	350	1.0	90	0	..	Abscessing tooth.
3–2	8,200	63.0	5200	28.0	2300	6.0	490	3.0	250	0		
3–9	8,700	58.0	4900	33.0	2900	6.0	520	3.0	260	0		
3–15	10,800	65.5	7100	26.0	2800	6.0	650	2.0	220	0.5	100	
3–16	11,700	57.5	7300	35.0	4500	5.5	700	1.5	190	0.5	60	
3–19	12,500	71.0	8900	22.0	2800	4.0	500	3.0	380	0	..	Unusually tired.

13. Dr. H., male, aged thirty-three years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remark.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	8,700	62.0	5400	27.0	2400	6.0	520	3.0	260	2.0	190	
1–13	9,600	63.0	6100	29.0	2800	6.0	580	1.5	140	0.5	50	
1–20	7,900	55.0	4400	29.0	2300	10.0	790	3.5	280	2.5	190	
1–27	10,200	57.0	5800	30.0	3100	7.0	710	5.0	510	1.0	100	
2–3	7,400	51.0	3800	37.0	2800	6.0	450	4.5	340	0.5	40	
2–10	7,800	57.0	4500	31.0	2600	7.0	550	4.5	350	0.5	40	
2–17	9,000	63.0	5700	28.0	2500	5.0	450	3.5	320	0.5	40	
2–24	9,600	52.0	5000	32.0	3100	10.0	960	4.0	380	2.0	190	
3–2	11,000	62.0	6800	24.0	2700	9.0	990	4.0	440	1.0	110	Laryngitis for 24 hrs., voice husky.
3–19	9,100	52.0	5200	28.0	2600	10.0	910	3.0	270	2.0	180	
3–15	11,200	57.5	6400	33.0	3700	6.0	680	2.5	280	0.5	60	
3–16	7,600	56.0	4300	33.0	2500	7.0	530	3.5	260	0.5	40	
3–20	7,100	59.0	4200	31.0	2200	6.0	430	4.0	280	0		

* The total cells in all of the charts are accurate to within 100 cells for the neutrophils and lymphocytes and within 10 cells for the other cell types.

GROUP III.—(FIRST 6 COUNTS 9.30 TO 10.15 AM..; REMAINDER OF COUNTS 2.30 TO 3.15 P.M.*

14. Mr. S., aged eighteen years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	6,700	61.0	4100	27.0	1800	2.0	600	2.0	140	1.0	70	
1–13	6,200	47.0	2900	40.0	2500	10.0	620	3.0	180	0		
1–20	7,700	54.5	4200	35.0	2700	9.0	690	1.5	120	0		
1–27	6,300	42.5	2700	36.5	2300	16.5	1040	3.5	220	1.0	60	
2–3	6,400	53.0	3400	36.0	2300	8.0	510	2.5	160	0.5	30	
2–10	7,900	56.5	4500	30.0	2400	11.0	870	2.0	160	0.5	40	
2–17	6,000	61.0	3600	30.0	1800	8.0	480	0.5	30	0.5	30	
P.M.												
2–24	8,400	63.0	5300	25.0	2100	7.0	590	4.0	340	1.0	80	Coryza.
3–2	7,400	63.0	4600	26.0	1900	8.0	590	2.0	150	1.0	70	
3–9	5,700	51.0	2900	35.0	2000	11.0	630	3.0	170	0	..	Coryza last 2 days.
3–15	6,400	52.0	3300	40.5	2600	5.0	320	2.0	130	0.5	60	
3–16	6,500	55.0	3600	35.0	2300	8.0	520	2.5	160	0.5	60	
3–19	11,400	78.0	8900	14.0	1600	6.5	740	1.5	170	0	..	All-night party Sat. night; to bed 2 A.M. Sun. night; feels "all in."
3–20	11,400	72.0	8200	18.0	2000	9.0	1010	1.0	120	0	..	Feels much better after 10 hrs. sleep.

15. Miss W., aged thirty-four years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	8700	64.0	5600	25.0	2200	6.0	520	4.0	350	1.0	90	
1–13	6300	53.0	3300	34.0	2100	9.0	570	3.5	320	0.5	30	
1–20	7800	57.0	4400	33.0	2600	6.5	510	4.0	310	0.5	40	Ac. coryza and laryngitis 14" to 16"; temp. 102; feels alright now.
1–27	8400	59.0	5000	31.0	2600	7.5	540	1.5	130	1.0	40	
2–3	7600	55.0	4200	33.0	2500	8.0	610	4.0	300	0		
2–10	8100	56.0	4500	33.0	2700	7.0	570	4.0	320	0	..	Menses.
2–17	7500	51.0	3900	41.0	3100	5.0	380	3.0	230	0		
P.M.												
2–24	8800	54.0	4700	35.0	3100	8.5	750	2.5	220	0		
3–2	8500	57.0	4800	33.0	2800	6.5	550	3.0	250	0.5	40	
3–9	7300	58.0	4200	33.0	2400	6.0	440	2.5	180	0.5	40	Coryza.
3–15	7800	52.5	4100	35.0	2700	8.0	620	4.0	310	0.5	40	
3–16	8500	53.0	4600	38.0	3200	6.0	510	2.5	210	0.5	40	
3–19	9800	52.0	5100	39.0	3800	8.0	780	1.0	100	0	..	Hard manual labor, Sat. P.M. and Sun.
3–20	7300	53.0	3900	38.0	2800	6.0	440	3.0	220	0		

16. Miss E., aged twenty-five years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	7900	60.0	4700	39.0	2400	5.0	400	4.5	360	0.5	40	
1–13	9600	58.0	5600	32.0	3100	7.0	670	3.0	290	0		
1–20	7700	55.0	4200	30.0	2300	9.0	690	4.5	350	0.5	40	
1–27	8400	56.0	4700	34.0	2800	7.0	590	2.5	210	0.5	40	Menses.
2–3	8800	56.0	4900	32.0	2800	7.0	620	4.5	400	0.5	40	
2–10	6300	55.0	3500	35.0	2200	5.0	320	4.0	250	1.0	60	
2–17	8700	56.0	4800	28.0	2400	9.0	780	6.5	570	0.5	40	
P.M.												
2–24	7800	60.0	4700	27.0	2100	10.0	780	2.5	200	0.5	40	Menses.
3–2	8500	54.0	4600	34.0	2900	6.0	510	5.5	470	0.5	40	
3–9	7900	57.0	4500	31.0	2400	7.0	550	4.5	360	0.5	40	
3–15	7800	62.0	4800	25.0	2000	9.0	700	3.5	280	0.5	40	
3–16	8100	57.0	4600	30.0	2400	8.0	650	5.0	410	0		
3–19	9600	55.0	5300	35.0	3300	5.0	480	4.0	390	1.0	100	
3–20	7400	53.0	3900	34.0	2500	10.0	740	3.0	220	0		

17. Mr. H., aged seventeen years.

Date.	Total.	Polymorphonuclears.		Leukocytes.		Mononuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1–6	8,100	47.0	3800	40.0	3200	6.0	480	6.0	480	1.0	80	
1–13	8,400	52.0	4400	37.0	3100	5.0	420	6.0	500	0		
1–20	10,000	45.0	4500	40.0	4000	9.0	900	6.0	600	0		
1–27	8,700	47.5	4200	38.0	3300	9.0	780	5.0	430	0.5	40	
2–3	7,100	51.5	3700	36.0	2500	9.0	640	3.0	210	0.5	40	Coryza.
2–10	7,800	51.0	4000	36.5	2800	9.0	700	3.0	230	0.5	40	Coryza.
2–17 P.M.	8,600	63.0	5400	28.0	2400	5.0	430	3.5	300	0.5	40	
2–24	7,000	52.0	3600	36.0	2500	7.0	490	5.0	350	0	..	Coryza.
3–2	8,600	57.0	4900	35.0	3000	5.0	430	2.5	210	0.5	40	
3–9	8,300	46.0	3800	43.0	3500	7.0	580	4.0	430	0	..	Coryza.
3–15	7,400	51.5	3800	38.0	2800	8.0	590	2.0	150	0.5	40	Mild laryngitis.
3–16	8,100	48.0	3900	40.0	3200	6.0	480	5.0	400	1.0	80	
3–19	8,400	61.0	5100	33.0	2800	4.0	330	1.5	130	0.5	40	
3–20	6,900	41.0	2800	46.0	3100	8.0	550	5.0	340	0		

* The total cells in all of the charts are accurate to within 100 cells for the neutrophils and lymphocytes and within 10 cells for the other cell types.

Epicrisis. Upon analysis the data given above show many points of interest. No individual had a constant leukocyte count, either totally or differentially. Some individuals did not vary over 3000 (Mrs. C.) in their total counts, while others varied over 8000 (Dr. S.). In the differential counts one person did not vary over 7 per cent (Miss E.), while another varied over 30 per cent (Mr. S.). Because of these variations, it seemed of value to establish the *mode*, rather than the average, of the whole group. Chart I gives the graphs representing the total and the differential counts.

With regard to the total counts, it is noted that the largest number of counts were between 7000 and 8000. There were 172 counts between 6000 and 9000, with 12 counts below 6000, and 57 above 9000. This shows that, in spite of the variations, one may consider, as is usually done, that a total count between 6000 and 9000 is the usual normal, while counts above or below this are unusual and may be considered abnormal.

The neutrophil graph shows the largest number of counts between 55 and 59 per cent. There were 167 counts between 50 and 64 per cent, while below 50 per cent there were 39 counts, and above 64 per cent there were 35 counts. One may then consider that it is abnormal to have the neutrophils below 50 or above 64 per cent.

With regard to the lymphocytes, there were 183 counts between 25 and 39 per cent, with the largest number of counts between 30 and 34 per cent. There were about an equal number of counts below 25 and above 39 per cent. It would appear, then, that a lymphocyte percentage below 25 or above 39 may be considered abnormal.

The mononuclear leukocyte (the monocyte of Naegeli, and the endothelial leukocyte of Mallory) shows a plateau at 6 to 9 per

cent, with 176 counts within this range. There were a few more counts above 9 than below 6 per cent, but one may regard a percentage below 6 or above 9 as unusual and therefore abnormal.

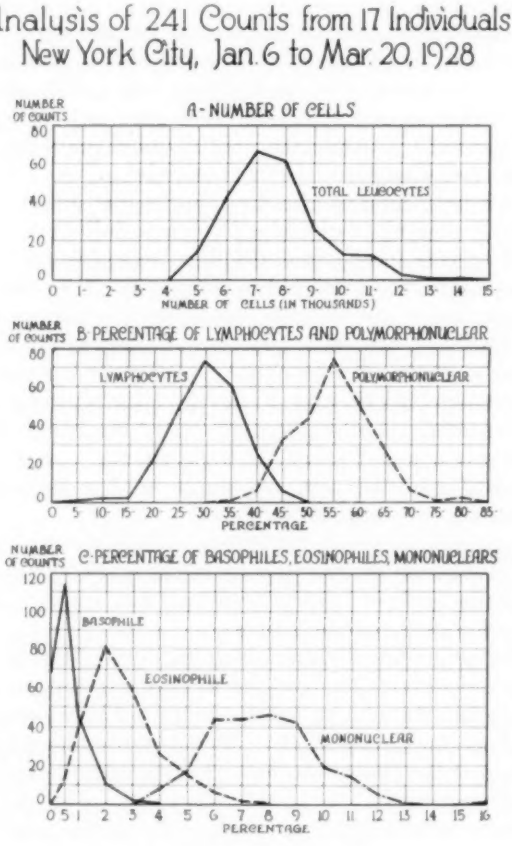

CHART I.

The normal eosinophil percentage appears to be between 1 and 3, and the basophil percentage 0.5 to 1. In the counting of 400 cells there were about one-third of the preparations which showed no basophils, while every count showed at least 0.5 per cent of eosinophils.

There does not appear to be any appreciable or constant variation between the morning and afternoon counts. It is recognized, of course, that these counts were taken at a relatively fixed time in the morning and in the afternoon. What variations might have occurred at other time intervals were not determined. The data here given show no evidence of a digestion leukocytosis. Just as

high counts were obtained in the morning as in the afternoon. (Compare Miss H. with all the counts in the morning, and Dr. L. with all the counts in the afternoon.)

An analysis of the counts taken during an ordinary "head cold" or a mild laryngitis shows no constant change. Most of the counts showed no marked change from the normal variation, while a few showed considerable variation. It may be stated that in this study no evidence was adduced to support the belief that ordinary mild infections of the upper respiratory tract have any influence on the leukocytic picture. The more severe infections may alter the leukocytic picture considerably. (Dr. S. last count.)

There does not appear to be any appreciable difference between the leukocyte content of the blood in the adult male and female. From the relatively small amount of data here presented the menses does not appear to affect the leukocytic picture in normal women.

A marked change can occur in the leukocytic picture of an individual without any evidence, clinical or otherwise, of an infection being present. Dr. B. developed a typical septic leukocytic picture after eating spoiled food. Mr. S. developed a typical septic leukocytic reaction after an all-night party which probably carried with it an abnormal demand upon his body tissues. Neither of these individuals had any of the signs or symptoms of an infectious process at the time the counts were taken.

Mrs. C. proved to be of interest in that she developed a very acute pityriasis of the greater portion of her body. The only appreciable alteration in her leukocytic picture was a rise in the eosinophils during the course of the disease.

Because of her relatively high leukocyte count Miss H. was asked to decrease her activities and to get at least eight hours of rest for two nights before the fifth and sixth counts. These counts were the lowest she had during the study. Whether the change in activity was the cause of the change in the leukocyte count is unknown, but it is at least suggestive.

Dr. S. showed the highest percentage of mononuclear leukocytes at the time he had an abscessed tooth. Mr. S. showed a mononuclear leukocyte count of 16.5 per cent without any clinical evidence of an infection being present at the time. Miss W. had the highest leukocyte count following strenuous physical exertion over the week-end, without there being any evidence of an infection. Dr. B. had the highest count twenty-four hours after an all-night vigil at an obstetric case.

There does not appear to be any greater variation in counts taken daily than in counts taken weekly in normal individuals. Where there occurred a greater fluctuation in the daily counts than was seen in the weekly counts an explanation for this change could be obtained. Whether the explanation offered really accounts for the alteration observed is, of course, a matter of conjecture.

Discussion. No originality is claimed for the differential classification of the leukocytes as used in this article. It is a grouping that has been extensively used in clinical practice for some years. The main purpose of the classification was to simplify as much as possible the number of cell types. It is admittedly incomplete, due largely to our incomplete knowledge of the exact origin, structure, developmental cycle and function of the different leukocyte types. Until such knowledge is completed, it seemed best to the author to adopt the simplest classification and technique possible.

There may be a difference of function or in age between the small and the large lymphocyte, but until such differences are fully established it would seem valueless to separate these cells into two groups.

By the use of a supravital technique differences in the finer structure of the monocyte and the clasmatocyte may be demonstrated. Until it is well established that these cells are of different origin and have different functions it would seem best to group them together as mononuclear leukocytes. Because of the similarity of the cytoplasm, as seen in preparations made with Wright's stain, of the transitional leukocyte and the monocyte and clasmatocyte, this cell has also been included in the group of mononuclear leukocytes.

There has been no attempt to classify the polymorphonuclear neutrophils according to the lobulations of the nucleus. Such a grouping gives valuable information relative to the demand for cells of this type. Such a study is not included in the present article which deals with the leukocyte content of the blood as a whole. Whether one chooses to use the method of Arneth,[7] of von Schilling[8] or of Pons and Krumbhaar[9] is a matter of personal preference. The method of Pons and Krumbhaar, because of its simplicity, has an especial appeal to the routine worker.

It is doubtful if there exists an individual who has an absolutely stable leukocytic picture. If this be true then one must accept as a normal an individual in good health with no demonstrable variation from the average as far as physical or other findings are concerned. But even here an unrecognized pathologic condition may exist. One might postulate that if there were no damage to or alteration in tissue, either by infectious or noninfectious agents, there would be no need for leukocytes to exist in the circulating blood. Since such a condition is unobtainable with life as it exists today, one may again postulate that the leukocytes may be taken as an index of the status of the tissues in their complex environment. If that, in a sense, be true, then one could hardly expect to find any two average normal individuals with exactly the same leukocytic formula at the same time, unless those individuals were existing under exactly the same conditions. We believe, as Miller[3] has stated, that the normal leukocytic picture of a community, and, if possible, of the individual, should be established if one is to get the proper interpretation of a leukocyte count in a pathologic process.

To illustrate, take two individuals, Mrs. C. and Miss W. Their

total counts were approximately the same when considered as a whole. Mrs. C. consistently had a neutrophil count above 60 per cent, while Miss W. had a neutrophil percentage below 60. In case Miss W. developed an acute appendicitis she might not run over 70 per cent neutrophils, whereas Mrs. C., under the same condition, might run over 80 per cent. Their total counts might, on the other hand, be similar. Or, again, take Dr. H., who had low total counts, and Miss H., who had high total counts. The differential percentage in each instance showed about the same range in variation. If Dr. H. developed acute appendicitis he might not have a total count over 10,000, which would be just as abnormal for him as it would be for Miss H. to have a total count of 15,000 to 20,000 under the same condition.

Our findings differ in certain aspects from the accepted textbook teaching. The total counts are the same. The eosinophils and basophils correspond. The percentage of neutrophils is lower, of lymphocytes and mononuclear leukocytes higher. Our findings agree in this respect with Bunting,[1] Stetson,[2] and others. They agree with Miller,[3] except that we have found the mononuclear leukocytes higher.

The reports of Sabin[4] and her co-workers, of Shaw,[5] and of Fletcher and Mitchell[6] have stressed the variation of the leukocyte counts in different periods during the day. Sabin, *et al*,[4] have concluded that there is practically an hourly rhythm and Shaw[5] has found that there are diurnal tides in the leukocyte content of the blood. From these reports it would seem essential that blood counts be taken at relatively the same time of day if any reliance is to be placed on their significance.

It seemed to us that, since this variation occurs, it was fully as important to know how great a fluctuation might occur in a relatively short space of time. Consequently we took three normal individuals and did counts at three- and five-minute intervals for a period of one hour or two hours. The graphs shown in Charts II and III give the results of this study. To have constancy of technique the author took all of the blood samples and did all of the counts. The samples were "staggered" in such a manner that no knowledge was obtainable as to the sequence of events until the entire study of each individual was completed. We felt it desirable to rule out all personal factors.

The author had followed the leukocytic picture of these same individuals over a period of several months, the blood having been taken at the same time of day as the short interval counts were made. When a comparison between the record of several months was made with that of one or two hours it was found that these individuals showed just as great a variation in their counts in a period of one hour as they had shown over a period of several months.

It is interesting to note that the greatest fluctuation in the total counts would have been missed had the examinations been made at

longer intervals. And it would seem plausible that had intervals of shorter duration been used still other variations would have been found.

A critical analysis shows that the time interval of greatest fluctuation was different in each individual. In one case the time interval was twelve minutes, in another twenty minutes, and in the third the

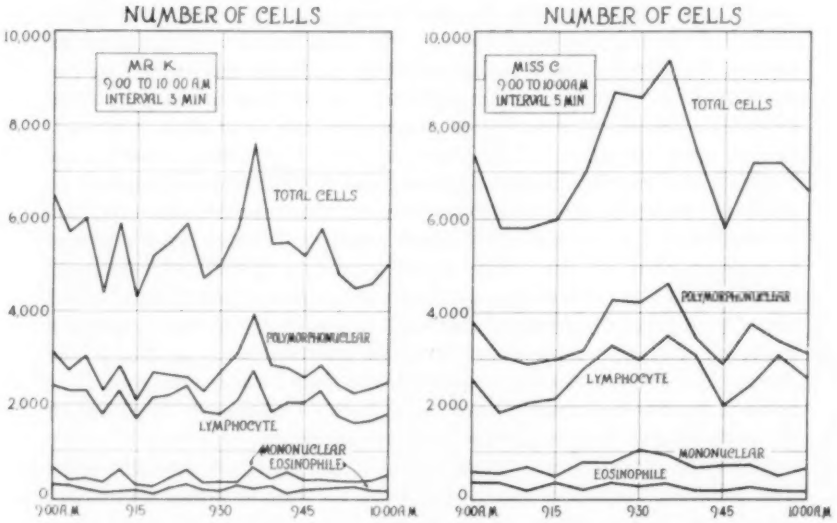

CHART II.

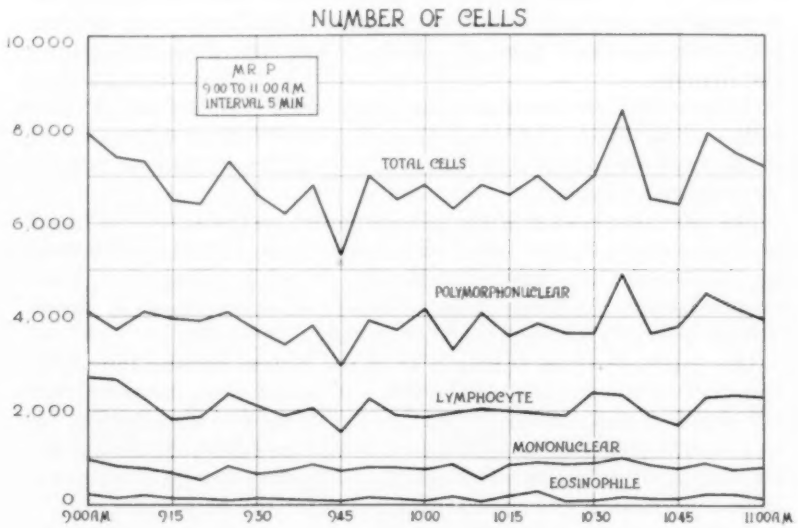

CHART III.

interval was fifty minutes. One grants that the fluctuation of a few hundred cells may be due to technical error, but a difference of over 2000 cells is due to some factor other than technical error. These observations do not appear to support the contention of Sabin, *et al.*[4] that there is an hourly rhythm in the leukocyte curve, unless each individual has a different rhythm.

The report of Shaw relative to the diurnal tides of the leukocytes is of considerable interest in relation to the variation in a short period of time as observed by us. We have found as great a variation in the total counts within an hour as Shaw has shown in the diurnal tides. Our technique differed only in that he used but one pipette, whereas we were forced, because of the short time intervals, to use many pipettes. The same pipettes were used in each case studied, and the highest and lowest counts did not correspond to the same pipettes. So that it would seem that our results could not be explained by the use of different pipettes. From Shaw's report it appears that on the whole there were two periods of relatively long duration in which the counts were consistently higher than at other periods of the same duration. Since there occurs as great a fluctuation in the leukocyte counts within an hour as Shaw has shown in a twenty-four-hour period, one is led to wonder just how great a fluctuation might have been found had counts been taken at short intervals when the tide was at its height.

The differential counts showed less variation than the total cells. The greatest variation was 10 per cent, so that it would seem that the differential distribution of the cell types is more constant than are the total cells. A careful analysis shows, however, that there is a variation to a mild degree, so that at one time the increase or decrease was due largely to lymphocytes, at another time to neutrophils, and at a third time all cell types had contributed equally to the change.

This study shows that a normal individual, (studied under carefully standardized conditions) may show a variation of 50 per cent in the total count, and of 10 per cent in the differential count, IN LESS THAN HALF AN HOUR.

We have observed that the place from which the sample of blood is taken—finger or ear—has no influence on the differences observed in the counts, providing free-flowing blood is obtained. Four counts have been taken from a single puncture wound at three-minute intervals with less than a variation of 500 cells.

One might theorize at length as to the factors causing the variation that occurs in leukocyte counts. It would seem, however, that the simplest explanation is that there is an uneven distribution, up to a certain point, of the leukocytes, totally and differentially, in the circulating blood. For, after all, the body does not have a central collecting, mixing and distributing point for the leukocytes.

Conclusions. 1. A variation of 100 per cent in the total leukocyte count and 30 per cent in the differential may be found, even in a

carefully standardized study, in an average healthy individual in the course of weeks, without any clinical disease being manifest. This does not signify that there may not be an abnormal condition present in the body tissues. The least variation found in an individual during the period of this study was 30 per cent in the total leukocyte count and 7 per cent in the differential.

2. In the majority of instances mild infections of the upper respiratory tract caused no significant change in the normal leukocytic variation.

3. There is no constant difference between the leukocyte counts in adult males and females.

4. Menstruation does not appear to alter the leukocytic formula in normal women.

5. A septic leukocytic formula can develop in a normal individual without any clinical evidence of an infection being present. This reaction probably is caused by a non-infectious chemical alteration in the tissues.

6. Normal individuals can show as great a variation in their leukocyte counts in an hour as they show in daily or weekly counts taken over a considerable period of time.

7. It appears that the variation in the leukocyte count over a relatively short space of time is due to an uneven mixture, totally and differentially, of the leukocytes in the circulating blood. It does not appear to be rhythmic in nature, unless each individual has a different rhythm.

8. The greatest value of the leukocytic formula in pathologic alterations of the tissues can be obtained only when the normal leukocytic formula for a community and for an individual has previously been established. A normal person tends to maintain a leucocyte level, both totally and differentially, within certain limits under normal conditions.

9. The leukocyte MODE of the group of normal individuals reported in this study is as follows: Total count 6000 to 9000; differential count—neutrophils, 50 to 64 per cent; lymphocytes (large and small types), 25 to 39 per cent; mononuclear leukocytes (monocytes, endothelial leukocytes, transitional types), 6 to 9 per cent; eosinophils, 1 to 3 per cent; basophils, 0.5 to 1 per cent.

NOTE.—I desire to express my appreciation of the coöperation of Dr. A. S. Knight, Medical Director, and the members of the Medical Division of the Metropolitan Life Insurance Company in New York City and at Mt. McGregor, N. Y., in arranging for this study and in being willing to be the subjects for study.

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MARKED MONOCYTOSIS ACCOMPANIED BY A NEUTROPHILIC LEUKOPENIA FOLLOWING ANTISYPHILITIC TREATMENT.

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The following case is reported as a type of reaction following antisyphilitic treatment in which the changes in the white blood cells were of great interest.

Case Report.—M. W., V. U. H. No. 5306, a colored female, aged twenty-four years, single, was admitted to the medical wards on October 26, 1927, with the complaint of chills, fever and sore throat. The past history was negative except for a sore throat four years previously. In July, 1927, she developed a skin rash but denied having had a primary lesion. She was first seen in the out-patient department on September 27, 1927, where a diagnosis of secondary syphilis was confirmed by the serum reaction, and treatment was instituted. On October 4, she was given 0.6 gm. of neoarsphenamin intravenously and 0.065 gm. of bichlorid of mercury intramuscularly and in addition saturated solution of potassium iodid, 20 drops to be taken orally three times a day, was begun. There was slight soreness at the site of the mercury injection but no further discomfort. On October 11, the injections of neoarsphenamin and mercury were repeated. The following night, October 12, the patient felt chilly and had one "hard chill," but on rising in the morning felt quite well and returned to work. On October 18, because of the reaction the preceding week, 0.6 gm. of sulpharsphenamin was given intramuscularly instead of the neoarsphenamin, while the mercury and iodides were continued as before. Immediately following this third treatment she felt faint. That evening she began feeling badly, a condition which became progressively worse until entry to the hospital, and there were associated fever (high fever, as the patient said), myalgia and repeated daily chills. On October 24, two days before entry and six days after her last treatment, her throat became sore, starting with sharp pains which increased until dysphagia was definite.

Examination on entry October 26, showed the patient to be alert, the skin hot, the temperature 101.6° F., pulse rate 120 per minute and respiratory rate 22 per minute. The skin showed a fading secondary syphilitic rash but no petechiæ, ecchymoses or jaundice. The eyelids were puffy. The epithrochlear, axillary, cervical and inguinal lymph nodes were moderately enlarged. The tonsils were swollen and red and there was a gray exudate on each. The tonsillar glands were enlarged and extremely tender but showed no sighs of suppuration. The lungs were clear. The heart showed only a tachycardia. The liver and spleen were not felt. No vaginal or anal ulcers were seen. Neurologic examination was negative. Urine examination and phenolsulphonphthalein excretion were normal. A smear from the tonsils showed very few cells, none of these being of the polymorphonuclear group, and there was no predominating organism. Throat culture yielded a mixed flora with predominance of hemolytic streptococci. The blood culture was sterile, the Wassermann reaction positive. The blood studies on entry showed a moderate secondary anemia, the red blood count being 3,420,000 per c.mm. and the hemoglobin estimation (Sahli) was 75 per cent. The leukocyte count was 7950 per c.mm. (subsequently a

leukopenia was found) but a differential study showed a complete absence of the polymorphonuclear group. The smear did show, however, numerous platelets, many of which were quite large. More complete blood studies are given below in the discussion.

The patient's course was one of uneventful recovery and only symptomatic treatment was given. Sodium thiosulfate was withheld because of the steady improvement. The temperature reached the highest point, 103.6° F., the day of admission and returned to normal on the third day of hospitalization. Antisyphilitic treatment in the form of mercury inunctions and potassium iodid by mouth was resumed on November 2.

Examination on discharge from the hospital on November 5, showed a chronic tonsillitis, a faded secondary syphilitic rash, general glandular enlargement and a positive Wassermann. The out-patient record indicated no further symptoms following the treatment as outlined and the last blood counts have been normal.

Discussion. There are two points of especial interest in this case. The first is a reaction following antisyphilitic treatment characterized by symptoms of a generalized infection, a necrotic tonsillitis and a blood picture showing a mild secondary anemia, a leukopenia and an apparently complete suppression of the polymorphonuclear group of cells. The second is that while there is distinct evidence of systemic poisoning with a temporary disappearance from the circulating blood of one type of leukocyte, there is also evidence of stimulation of another type, the monocyte.

The general reaction and the clinical picture presented in this case classifies it as "agranulocytic angina." Schultz[1] states that there is a disease of unknown etiology, occurring in middle-aged females, fatal in its outcome and characterized by a febrile reaction, a necrotic tonsillitis and a leukopenia with suppression of the granulocytic series. To this, he gives the name agranulocytic angina. Schultz and Jacobowitz[2] make a further report based on 10 of their own cases and 13 from the literature and modify the first report by noting that it is not confined to females, that there is normal erythropoiesis, an absence of a hemorrhagic tendency and no thrombopenia. The review of Kastlin[3] is complete and summarizes the findings in 43 cases, giving tables of the results. Case reports and shorter summaries may be found in the recent literature. The consensus of opinion at present is that this condition is not a disease entity as at first supposed, but that it is an expression of a reaction of unknown etiology. Feer[4] suggests "sepsis agranulocytotica" as a more comprehensive term but this seems to add little to the better understanding of the condition.

Turning to the tissue response in the case reported, there are several interesting points for consideration and correlation with the findings in other reported cases and also with our knowledge of the effect of arsenic, benzene and the arsenobenzols on the leukopoietic "centers." At the same time a more important problem presents itself, namely, the type of the cellular response.

Table herewith gives the blood findings in the case under discussion and while it is self-explanatory certain points should be emphasized.

TOTAL AND DIFFERENTIAL BLOOD COUNTS.

Date.	Red blood count, per c.mm.	Hemoglobin, Sahli, per cent.	White blood count, per c.mm.	Polymorphonuclears.			Lymphocytes small, large and intermediate, per cent.	Monocytes, per cent.	Ratio of monocytes to lymphocytes.	Myelocytes, per cent.	Platelets, per c.mm.	Clotting time, min.	Bleeding time, min.
				Neutrophiles, per cent.	Eosinophiles, per cent.	Basophiles, per cent.							
Oct. 26, 1927	3,420,000	75	7950	0*	1.0	0	37 ?	62 ?	...	0			
Oct. 27, 1927	3,695,000	65	4680	3.5	1.0	0	34.5	61.0	1.8	0	182,500	7	1.5
Oct. 28, 1927	3,850,000	65	4760	16.0	1.0	1	41.5	39.0	0.9	1.5			
Oct. 29, 1927	4,300,000	65	4440	29.5	3.0	0	40.5	26.5	0.7	0.5			
Oct. 31, 1927	3,800,000	..	5040	51.0	2.0	0	34.5	12.0	0.4	0.5			
Nov. 3, 1927	3,270,000	63	4920	53.0	4.0	0	34.0	6.0	0.2	3.0			
Nov. 4, 1927	4,690,000	64	7840	60.0	2.0	0	29.5	8.5	0.3	0			
Nov. 28, 1927	.....	..	7720	68.5	1.5	0	22.5	7.5	0.3	0			
Jan. 19, 1928	4,400,000	75	7800	73.0	0.5	0	18.0	8.0	0.4	0.5			

* Wright's stain was used on their preparation. Subsequently the various leukocytes were differentiated by supravital staining.

It is evident that there was at first a moderate leukopenia followed by a gradual return of the white blood count to normal. The first differential study was made with Wright's stain. It showed no polymorphonuclear cells but did show the presence of a mononuclear cell which was difficult to classify into the customary groups. The first study by the supravital method revealed an almost complete suppression of the polymorphonuclear group, a total lymphocyte count slightly under normal and the number of monocytes considerably increased. These monocytes were definitely stimulated, being specifically of the type of monocytes seen in catarrhal jaundice and not of those seen in tuberculosis. Both types of monocytes have an increase in the vacuoles or bodies staining with neutral red. They differ, however, in that these vacuoles are much smaller and more numerous in tuberculosis (Cunningham, *et al.*[5]) while those in catarrhal jaundice are even larger than the normal. Subsequent differential studies showed a gradual return of the polymorphonuclear cells to the circulating blood with the appearance of myelocytes as well, the lymphocytes returned to a total number higher than normal while the monocytes fell practically parallel with the reappearance of the polymorphonuclear leukocytes, and at the same time qualitatively resumed their normal characteristics. The last observations indicated a normal blood picture.

The red blood count and hemoglobin determination showed a moderate secondary anemia without any notable qualitative changes in the cells and during the period of observations the total number of red cells returned to normal while the hemoglobin showed evidence of a "lag." In the first smear, the platelets were seen in abundant numbers, the total count on October 27, being 182,500. The clotting time, determined by the method described by Minot and Lee[6] was seven minutes with a good retraction and a firm homogeneous clot formation. The bleeding time was one and a half minutes and the icteric index was five.

The point of particular interest is that, whatever the exciting cause, there was a remarkable stimulation qualitatively and quantitatively of the monocytes, a depression of the total leukocyte count, a complete suppression of the polymorphonuclear cells and practically no change in the number of lymphocytes. This picture is practically identical with the response to arsphenamin noted by Evans.[7] Moore and Foley[8] cite a case of arsphenamin poisoning in which there was a febrile reaction, an ulcerative stomatitis and a leukopenia with a relative increase in the large lymphocyte—transitional group of cells and depression of the polymorphonuclears. Case 7 of Krumbhaar's[9] series of leukemoid blood pictures presents several interesting points of similarity.

The factor causing the blood reaction is not obvious. The possibilities are that it is the arsenic, the benzene or the combination of the two in the form of the arsenobenzols. By far the majority of the

reactions, following the use of the arsenobenzols, in which there is a change in the blood cells is a general bone-marrow aplasia. Dodd and Wilkinson[10] summarize 24 cases of poisoning during the antisyphilitic treatment giving the major blood findings. Their summary demonstrates that aplasia is common. In the report of the Arsphenamin Committee of the Medical Research Council[11] no definite evidence is given of a leukotoxic action following the administration of the arsphenamin group of drugs. The action of benzol as a leukotoxin has been worked out by Selling.[12] Clinical observations of benzene as an industrial poison are numerous and Weiskotten and his coworkers[13] have published a series of papers on the action of benzol. In these studies a polymorphonuclear suppression was followed by a suppression of all the blood cells. Textbooks of pharmacology do not speak of a leukotoxic action of the inorganic arsenic preparations despite the fact that Fowler's solution (Liquor potassii arsenitis) has been used for years in the treatment of anemia. The inorganic arsenic compounds are generally considered as stimulants to the red marrow and one would expect that any consistent action on the white blood cells would have been noted. In general, this has not been shown. However, 2 unpublished cases are recalled in which a leukopenia developed coincidently with the use of Fowler's solution and there was also a suppression of the polymorphonuclears, but with a relative and not an absolute increase in the mononuclear cells. After discontinuing the drug, the blood counts and differential studies in these 2 cases returned to normal. A review of 28 cases of accidental arsenic poisoning by Lawson, Jackson and Cattanach[14] shows in the surviving patients a leukopenia with a polymorphonuclear suppression and a relative increase in mononuclears at the end of five days with an evident tendency to establish a normal picture on the twelfth day. A few scattered reports indicate that a mild leukocytosis occurs in experiments on dogs in which arsenic was administered.

Many reports do not throw additional light on the underlying process of cell stimulation or cell depression because of the difficulty experienced in accurate cell differentiation. The white blood cells take on different characteristics under different stimuli and these changes are not easily recognized in fixed preparations. It would be of considerable interest to know what percentage of the mononuclear cells in the above-mentioned articles were lymphocytes and what percentage were monocytes. In the reported case, there is evidence that one type of white corpuscle may be suppressed, another type may be stimulated while a third type may be unaffected. This seems to indicate that, in adult life at least, the three types do not have a common parent cell.

Summary. The presented case shows an unusual, though not new, type of reaction to antisyphilitic treatment. Besides the interesting general reaction with septic tonsillitis there was a decided

action on the leukopoietic centers, in that a leukopenia was present with a depression of the polymorphonuclears and a stimulation of the monocytes. This type of case cannot with consistency be called agranulocytic angina in the sense that is usually attached to it. The causative factor is not evident inasmuch as arsenic, benzene and the arsenobenzol preparations occasionally all give rise to a similar picture, but the evidence seems to point to a poisoning by the benzene or arsenic rather than the conjugated arsenobenzol.

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ADENOMA OF THE ISLANDS OF LANGERHANS WITH ASSOCIATED HYPOGLYCEMIA.*

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and

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Adenomata of the islands of Langerhans have been described, cases of hypoglycemia have been observed clinically and a malignant tumor of the islands of Langerhans with hypoglycemia has been reported, but our search of the literature to date has failed to show a single benign tumor of the islands of Langerhans associated

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with hypoglycemia proved by antemortem blood studies.* Because of this finding, we have been particularly interested in the following case:

Case Report.—A. J., a colored male, married, aged forty-one years, truck driver by occupation, was admitted to the Pennsylvania Hospital on December 21, 1927, with the chief complaint of attacks of loss of memory. During the summer and fall of 1927 he had complained of a very queer feeling which could not be localized or accurately described but which apparently occurred more commonly during the middle of the day. He was not a heavy eater and his meals were very irregular. He was particularly fond of hard candy and always carried some in his pockets, and at times when he felt queer he would stop his truck and get something to eat. On one occasion he came home from work feeling poorly, but after lunch, while his sister was about to notify his employer of his illness he felt so much improved that he insisted on returning to work.

His attacks which consisted essentially of loss of memory seemed to come on gradually and to last on an average of one and a half hours. Between attacks, he was apparently perfectly normal. During the last week in November, he was arrested three times for driving his truck past signs although previously he had always been a careful driver and had never been arrested. On the day of admission to the hospital, he suffered from one of these attacks and on being brought to the hospital was found to be in coma, but within an hour and a half he had regained consciousness and was anxious to go home.

Physical examination done on arrival at the ward was essentially negative. The temperature, pulse and respirations were normal. The routine urine and blood examinations were negative except for a leukocytosis of 13,700. A provisional diagnosis of epidemic encephalitis was made. Blood Wassermann and Kahn tests were later reported negative.

He had a supper consisting of house diet and was apparently comfortable. At 5 A.M. on December 22 he was found to be comatose. There were no definite signs of a cerebrospinal lesion. Examination of the spinal fluid was negative except for the finding of 20 mg. sugar per 100 cc. of spinal fluid. The Wassermann and Kahn and colloidal-gold tests on this fluid were negative. The blood-urea nitrogen was 17 mg., the creatinine 1.5 mg. but the sugar was only 40 mg. per 100 cc. On the next two subsequent days, the twenty-third and twenty-fourth, the blood-sugar determinations proved to be 42 and 38 mg. per 100 cc. respectively. His coma continued and a bronchopneumonia developed forty-eight hours before death. The only important findings were the persistent low blood-sugars in spite of the administration of glucose intravenously, by gavage and rectum. The amounts of glucose given, however, were relatively small as can be noted in the chart (Fig. 1). Death occurred on the afternoon of the twenty-fourth, seventy hours after admission.

The anatomic diagnosis made at autopsy, which was performed ten hours after death, was as follows: (*a*) Extensive bronchopneumonia of both lower and the right middle lobes. (*b*) Generalized arteriosclerosis. (*c*) Chronic myocarditis and nephritis due to arteriosclerosis (both moderate in extent). (*d*) Associated with cerebral arteriosclerosis, evidences of meningeal and cerebral irritation were definitely present, manifesting themselves in the form of slight perivascular round-cell accumulations showing that some form of mild cerebral irritation or inflammation was present, the nature of which we were not able to determine.

* In a personal communication from Dr. W. Thalhimer, of Milwaukee, Wis., we have recently had the opportunity of hearing of a case quite similar to the one we are reporting.

Of particular interest, however, was a lesion in the pancreas. This organ measured 17 by 4.5 by 1 cm., was homogeneous in consistency, and grayish in color. Projecting above the surface on the anterior aspect of the pancreas (Fig. 2) close to the superior border at the junction of the middle and distal thirds was a round, circumscribed nodule measuring 15 by 7 by 16 mm. It was soft in consistency and reddish-brown in color. Its surface was lobulated. On section, it was found to be vascular and to be surrounded by a delicate fibrous capsule. Gross examination of the rest of the gland was negative and the adrenals, liver and pituitary were also negative grossly and microscopically.

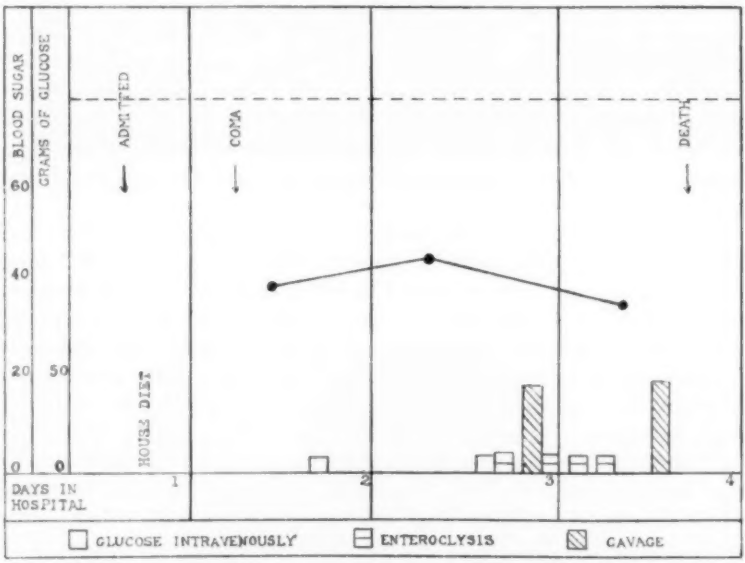

FIG. 1.—Diagram of the blood-sugar determinations in milligrams per 100 cc. The lower limit of normal blood-sugar values (80 mg.) is shown by the horizontal broken line at the top of the chart. The amount and manner of carbohydrate intake expressed as grams of glucose is also shown.

Microscopically, under low power, the tumor is partially separated from the surrounding pancreatic tissue by a fibrous tissue capsule (Fig. 3). In areas, however, both merge together gradually. Throughout the tumor the stroma in general is moderately developed although it is delicate in a few areas. The cells tend to have an alveolar arrangement surrounding blood spaces.

Under high power, the individual cell is polyhedral or cuboidal in shape with faintly granular eosin staining cytoplasm surrounding a small round nucleus rich in chromatin (Fig. 4). No zymogen granules are present and no mitotic figures seen. The growth is extremely vascular and the blood spaces do not appear to be lined with endothelium.

Associated with the adenoma there is a marked increase in size and in number of islands in the adjacent pancreatic tissue (Fig. 3). Bensley stains for island-cell differentiation and the biologic assay for the insulin content of both pancreas and adenoma (which was made through the kindness of Dr. D. A. Scott of the Connaught Laboratories of Toronto) failed because we had not fixed the tissues properly. From the morphologic appearance of the cells, however, we believe that they were of the beta type.

We are confronted, therefore, with a pancreatic lesion associated clinically with a diminution of the blood sugar and the question immediately arises as to whether or not we are dealing with an example of so-called "hyperinsulinism." In reviewing the literature on the question of hyperinsulinism, Harris[1] reports 5 cases of hypoglycemia in nondiabetic patients whose fasting blood sugars averaged 60, the lowest being 47 and the highest 67. The cardinal symptom in all these patients was weakness especially before the noon meal. Frequent feeding furnished great relief. Cammidge[2] reports a similar case in which the fasting blood sugar was 45. Attacks of giddiness were associated with this condition. Pemberton[3] reports 2 similar cases. None of these cases were fatal while under observation and therefore the conclusions were drawn from clinical findings only. Most of these authors seem to agree that so-called hyperinsulinism is perhaps a disease entity, recognizing however, that the liver, adrenals, pituitary and thyroid gland may play some rôle.

A splendid review of the subject of adenomata of the islands of Langerhans has been made recently by Warren.[4] Up to that time, only 20 cases had been reported in the literature. It is interesting to note that in 1 case only is there a history of diabetes and the lesions in the pancreas were mere subsidiary findings. The incidence is about equal in both sexes. The average age is fifty-seven years. Most of these cases were reported before the days of routine blood-sugar analysis. Hyperplasia of the surrounding islands associated with the tumor formation was reported in 5 cases. Cecil[5] concludes that these tumors are part of a generalized hyperplasia of the islands while Warren states that "the lack of correlation with other lesions is rather against the interpretation of these tumors as hyperplastic islands."

Wilder[6] has recently reported a case of carcinoma of the islands of Langerhans with metastases to the liver and lymph glands associated with hyperinsulinism and hypoglycemia. Alcoholic extracts of the tumor cells in the liver were found to be rich in insulin. He concludes, therefore, that the islet cells although they have undergone neoplastic change had retained the function of the parent cell.

Discussion. In our case, we have a lesion of the pancreas which may be regarded as an adenoma or as a greatly hypertrophied island. Its size, encapsulation and compression of surrounding pancreatic tissue favor the former view while the presence of many very large islands in the surrounding tissue suggest the latter condition. The question, as to whether hyperplasia of the islands is responsible for or secondary to the increased carbohydrate intake, is a debatable one. Hypertrophied islands in diabetics which from size alone might be considered adenomata have been described by Reitmann,[7] Herxheimer[8] and others. Gray[9] reports a case of insular hypertrophy and hyperplasia associated with a low blood sugar in an infant of a markedly diabetic mother and suggests that

FIG. 2.—Sagittal section through the tail of the pancreas, showing the encapsulated tumor protruding from its anterior surface. Magnification ×1.6.

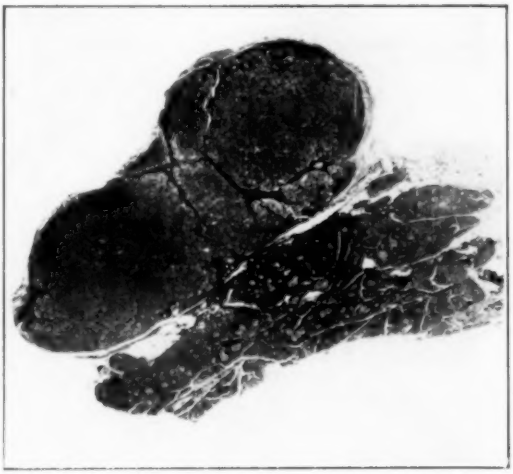

FIG. 3.—Low-power photomicrograph of the tumor and adjacent pancreatic tissue, in which the hyperplastic islets are seen.

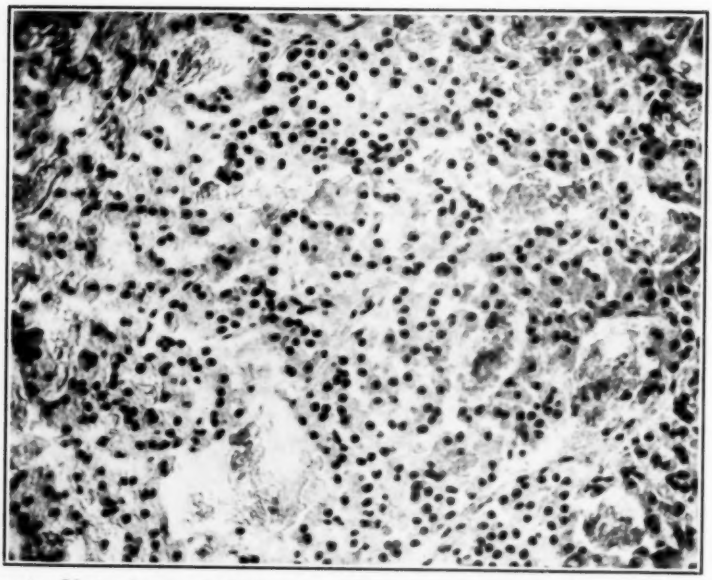

FIG. 4.—Photomicrograph, high-power, of the tumor. The cells have an alveolar arrangement surrounding blood spaces. Magnification approximately ×200.

the maternal blood sugar may be the stimulus which called forth the increase in insular tissue. On the other hand, the increased carbohydrate intake may have been necessitated by the hyperinsulinism. There is little doubt but that this was the condition in Wilder's case and the peculiar clinical history in our case is more favorable to this opinion. Undoubtedly, hypertrophy and adenomata of the islands of Langerhans may occur without any demonstrable disturbances in carbohydrate metabolism. In the 20 cases reported by Warren the pancreatic lesions were subsidiary findings with no apparent clinical significance. Our case would strongly suggest, however, that under certain conditions there is definite relationship between the adenoma and a particular symptom complex. This may be due to the fact that the tumor cells have retained the function of the parent cells. In this connection, it is well to recall parallel conditions in other glands of internal secretion, for example, adenomata of the hypophysis and thyroid where tumor formation is associated with definite disease entities.

Summary. 1. A case is reported in which periodic attacks of hypoglycemia were associated with loss of memory or consciousness in a patient who was found at autopsy to have a lesion of the island cells.

2. The lesion consisted of a large circumscribed nodule (adenoma) which was found to be wholly composed of island cells and islands in the remainder of the pancreas were found to be markedly hypertrophied.

3. The significance of this relationship between hypoglycemia and hypertrophy or adenoma formation of the islands is alluded to and it would seem to add further evidence toward the creation of a new disease entity.

We wish to express our very sincere thanks to Dr. John R. Paul, Director of the Ayer Clinical Laboratory, who both in the preparation and study of the material and by his helpful criticism and interest in the paper has made this presentation possible.

We are also indebted to Dr. John T. Bauer and Miss Mary Naylor for their kindness and coöperation in doing the photography.

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THYROTOXICOSIS FROM THE INTERNIST'S STANDPOINT.*

By Joseph L. Miller,
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The current literature on goiter is voluminous and one can scarcely hope to review it completely. New facts and theories are being constantly submitted. New discoveries may any day greatly modify and perhaps clarify our knowledge in this field, which at present is in a state of great confusion. We know very little of the pathologic physiology of hyperthyroidism and practically nothing of what excites the gland to this peculiar activity. Why will iodin convert a simple goiter into a toxic one and, in turn, tend to cause reversion of a toxic thyroid toward simple colloid goiter? Why is this relief at times temporary? Why does iodin fail to produce toxic symptoms, except in rare instances, in individuals with a normal gland? Why is hyperthyroidism, or in fact any form of goiter, so much more frequent in the female? Why do we occasionally see hyperthyroidism with a histologically normal gland? How can we explain the apparent presence in the same individual of both hypo- and hyperthyroidism? What about the group of patients with symptoms resembling mild hyperthyroidism with subnormal basal rates? Or another group, less common, with all the clinical manifestations of marked hyperthyroidism and normal rate, who, after a few weeks or months, develop a basal rate commensurate with the clinical findings? Why should a considerable number of hyperplastic hyperthyroids, after subtotal thyroidectomy, show a marked tendency to recur? Why is hyperthyroidism much more prevalent in regions where simple goiter prevails? What, if any, relation does the thymus bear to this disease? If we were only able to answer these questions it would illuminate many dark places and give us some understanding of this enigma.

The enlargement of the thyroid in infants, at puberty, and during pregnancy is considered physiologic—presumably a response to a greater need for its specific secretion. Strange to relate, the gland histologically in these cases bears a striking resemblance to the hyperplastic goiter of hyperthyroidism. Similar histologic changes are observed in dogs after lobectomy, and are referred to as compensatory hyperplasia. Although histologically closely resembling the gland of hyperthyroidism, the physiologic goiter does not give rise to toxic signs or symptoms. Some observers, however, believe that the instability of the nervous system at puberty is really a mild form of hyperthyroidism. Aschoff refers to some work done

* Read before the Chicago Society of Internal Medicine, May 28, 1928.

by Hellwig where he was able to demonstrate increased basal metabolic rate in this group of cases.

Iodin will, as a rule, prevent these physiologic hyperplasias. It will also prevent hyperplasia in dogs, following lobectomy, provided the amount of thyroid removed (according to Marine) does not exceed about two-thirds of the total gland substance. In both man and dog, after iodin, the hyperplasia disappears and the gland reverts to the colloid type which both biologically and anatomically is the nearest approach to normal that a previously hyperplastic thyroid may attain. During the hyperplasia, the flat or cuboidal epithelial cells lining the alveoli, hypertrophy—becoming columnar or cylindrical and at the same time increase in number, a true hyperplasia. The colloid is either greatly lessened or may entirely disappear from some alveoli. After iodin, there is a reversion to the normal cuboidal cell with reappearance of colloid.

Physiologic hyperplasia is wide spread and is not confined to goiterous districts. In goiterous regions, however, the response is more marked.

The amount of iodin required to prevent hyperplasia is exceedingly small. In Switzerland, the iodized salt which they find satisfactory contains 5 mg. of iodin per kilogram. They estimate that the average individual will consume about 3 kilograms of salt annually and he, therefore, receives about 15 mg. of the iodin. Iodized salt in this country contains 200 mg. of iodin per kilogram. This raises the amount consumed in a year to 600 mg. or 40 times that of Switzerland. It is estimated that the annual requirement of the thyroid under normal condition does not exceed 50 mg. It appears, therefore, that iodized salt in this country contains far too much iodin. The Swiss physicians claim that the amount of iodin we add to salt will convert many simple goiters into the toxic type, and there is a growing belief that this actually occurs in the United States.

Formerly, practically all the dogs used in the physiologic laboratories at the University of Chicago had goiter. Now, I am told by a member of this department that canine goiter has become rare, which he ascribes to the widespread use of iodized salt—the average dog living largely on table scraps.

With advancing years, the thyroid atrophies and may be reduced to one-half the normal size. Both epithelium and colloid are greatly lessened. This atrophy of age, however, must be taken into consideration in the surgery of the thyroid. We will be better able to determine whether subtotal thyroidectomy is a safe procedure when patients so treated have been followed to the three score years and ten.

Mobius' monograph on exophthalmic goiter, published in 1886, was the first clear exposition of this disease. Little has been added to the clinical syndrome as presented by him. No one has improved

on his definition of this disease—"Basedow's disease is an intoxication of the body due to abnormal activity of the thyroid."

The pathologic histology of the thyroid in hyperthyroidism has attracted much attention and it is quite generally accepted that there is not a single picture. Since we have outgrown, thanks largely to basal metabolism, the old classical triad of goiter, exophthalmos and tachycardia, we know that many of these patients have no material enlargement of the thyroid.

Two general types of gland may be recognized—the diffuse hyperplasia and the nodular or so-called adenomatous type. It is at present generally conceded that the adenomas do not arise from fetal rests; and, unlike these, may function much as normal thyroid tissue, having periods of hyperplasia followed by a resting stage. Aschoff believes adenomas arise from apparently normal thyroid tissue, especially that centrally located in the lobule. It is at present debatable whether the adenoma is a real tumor or merely a parenchymatous hyperplasia.

Some simple adenomas respond to iodin in the same manner as the hyperplastic thyroids. We know that a so-called toxic adenoma will respond quite as well to iodin as the exophthalmic type. De Quervain agrees with Aschoff that the adenoma may be capable of hypo- and hyperfunctioning just like the normal gland. In some cases they believe the hyperplasia is confined solely to the adenomas. More frequently, however, the adenoma is unchanged; the surrounding thyroid tissue alone being involved. In 16 cases of toxic adenoma, W. G. MacCallum[1] found only 1 in which the nodule showed the hyperplasia and infolding character of hyperthyroidism. In only 1 instance was the hyperplasia limited to the adenoma.

Recently W. F. Reinhoff and Dean Lewis[2] have studied the thyroid in 189 cases of so-called toxic adenoma. In 9 of these, the nodule resembled a true benign parenchymatous neoplasm, but in no instance did it participate in the hyperplasia which was present in the surrounding thyroid tissue. In 34 per cent, the nodules were due to colloid cysts. All of this group was found in long-standing cases, and they believe this change is due to overinvolution occurring during spontaneous remissions or following the use of iodin. These involuted nodules show hypertrophy and hyperplasia similar to that of the surrounding thyroid tissue. In the remaining 63 cases (58 per cent), the nodules were due to circumscribed hyperplasia of limited areas of the gland with intervening normal tissue. In these cases the hyperplasia was merely circumscribed rather than diffuse. All of this group showed a rather moderate degree of intoxication. If their findings are confirmed, the nodules found in toxic goiters may be true adenomas, overinvoluted tissue, or circumscribed areas of hyperplasia. With the available evidence, it would appear misleading to continue to use

the term "toxic adenoma." It is more accurate to say "hyperthyroidism with nodular goiter" or still better "thyrotoxicosis with nodular goiter."

The histologic picture in the hyperplastic gland in hyperthyroidism resembles quite closely that of the physiologic hyperplasia of puberty—the chief difference is one of degree; the hyperplasia being much more marked in hyperthyroidism. The superficial vessels became dilated thus accounting for the bruit. The gland is firm and when cut presents a uniform red dry appearance—the latter being due to lessened colloid. Histologically, it differs from the normal in the great reduction in colloid. The acini appear small; some of them may be practically obliterated. The epithelial lining often buckles, leading to papillary projections into the acinus. The cells have been transformed from the normal flat type into high cuboidal, columnar or even cylindrical forms—a true hypertrophy. In addition, there is marked hyperplasia, due to formation of new epithelial cells. This hypertrophy and hyperplasia accounts at least in part for the constriction of the acini. In addition, islands of lymphoid cells may be seen. Similar lymphoid areas may be observed in the ordinary colloid goiter and cannot be considered a special characteristic of the gland in hyperthyroidism.

If we were able to eliminate the cases of Basedow's with histologically normal glands, it would simplify the problem very much. It is true that in many cases there are islands of hyperplasia, with intervening normal gland tissue. However, those who have studied this question carefully admit that we may have typical hyperthyroidism without evidence of epithelial hyperplasia. Aschoff says that we may have hyperplasia without Basedow's and Basedow's without hyperplasia. This would suggest that hyperplasia is not essential to hyperthyroidism. We should bear in mind, however, that an exceedingly small amount of hyperplastic tissue may be responsible for marked intoxication. Not infrequently following a subtotal thyroidectomy, when the symptoms fail to abate the very small amount of thyroid tissue attached to the posterior capsule (too small to be detected by palpation) may cause the same degree of intoxication as the entire gland. Dr. Phemister recently showed a patient where, after subtotal thyroidectomy, the basal rate remained high—about +50. Several months later, a second operation was performed in order to determine whether a portion of the thyroid may have been overlooked. Two small pieces of tissue, the size of a pea, were found in the region of the lower poles and the blood-vessel entering these nodules was ligated. The basal rate promptly dropped to normal and the patient returned to work for six weeks, when the basal rate rose to +70 with return of symptoms. If such a small amount of tissue may cause intoxication, it is possible that Basedow's with reported normal thyroid, may contain small areas of hyperplasia which have been overlooked.

There is extreme variation in the iodin content of the normal thyroid. Bauman, and Zeit,[3] who first determined the iodin content of the thyroid, found the average amount to be about 6.6 mg. In the normal thyroid, however, variations were found from 1.7 to 27 mg.

Oswald determined the iodin in 119 normal glands in Switzerland with a variation of from 0.48 to 13.6 mg. He found the normal gland in Sweden did not differ in its iodin content from that of Switzerland—thus disproving the view held by some that the thyroid near the ocean contains more iodin. He examined 43 simple goiters in Switzerland; the iodin content varied from 11.7 to 26.9 mg. The colloid goiters had the largest amount; less in the parenchymatous type; and least in the adenomatous—while the total iodin was greater than in the normal the amount per gram of dried gland was less.

As a rule, the gland in hyperthyroidism contains relatively much less iodin than the simple colloid goiter, although the total iodin content may be greater than the normal gland. Marine states that the iodin content varies directly with the amount of colloid and inversely with the degree of hyperplasia. In other words, colloid is essential for the storage of iodin. Marine reports Basedow's thyroids with a higher percentage of iodin per gram of dried gland, than in colloid goiter. Oswald confirms this. We may conclude from this that deficient iodin in the gland is not an essential factor in hyperthyroidism.

There is considerable difference of opinion in regard to the iodin content of adenomas in hyperthyroidism. Marine believes the iodin content of the adenoma is less than in the surrounding tissue. De Quervain, on the other hand, states that he has seen adenomas with three times the amount of iodin present in the surrounding tissue.

The effect of administering iodin on the iodin content of the gland has been studied by Jansen and Robert.[4] Without previous iodin, the average percentage of iodin expressed in milligrams in the fresh normal gland was 9.39; colloid goiter, 4.87; mild hyperthyroidism, 5.64; severe hyperthyroidism, 6.81—showing a relative iodin deficiency in hyperthyroidism as compared to the normal, but a slight increase in the total iodin content of the gland.

The normal gland after iodin shows a relatively great increase in iodin. The simple goiter took up iodin much less readily than the normal gland, although there was both a relative and absolute increase. The gland in hyperthyroidism behaved in much the same manner as in simple goiter—a moderate relative and absolute increase; the milder the degree of intoxication, the less the increase in iodin.

They also studied the iodin content of blood. Without previous administration of iodin in colloid goiter, the iodin content of the

blood was about 30 per cent of normal. In Basedow's, the blood iodin was increased three-fold over the normal. There was no relationship between the amount of iodin in the blood and the iodin content of the gland. This would suggest that the Basedow's thyroid is lacking in ability to store iodin or, as the writers believe, there is an excessive production of thyroid hormone.

The blood in simple colloid goiter, after iodin, contained a great increase in iodin—showing that excessive iodin in the blood *per se* was not responsible for the intoxication. Some individuals with simple goiter, both colloid and adenomatous, who after iodin became toxic did not show relative or absolute increase in the iodin content of the gland. In other cases, the relative and absolute iodin content of the gland was increased, but there was no change in blood iodin. Apparently, there is a qualitative factor in the secretion which may or may not be iodin in nature.

Reinhoff[5] has studied the anatomic changes in the thyroid of Basedow's after iodin. A small piece of the gland was removed previous to the administration of iodin and compared with the sections at time of operation. After iodin, the gland became softer and somewhat smaller. The cut surface dripped with a glairy fluid which proved to be colloid. Cells showing mitotic figures disappeared. The hypertrophy and hyperplasia of the epithelial cells was lessened or in certain areas had entirely disappeared. The vascularity was less; some of the vessels were collapsed from pressure of colloid in the distended acini. This supports Marine's view that the action of iodin in hyperthyroidism is mechanical, interfering with the escape of the secretions into the circulation. In case the thyroid contained an adenoma, Reinhoff found it showed increase in the colloid.

Cattell,[6] studied a series of the thyroids where the patient had preliminary iodin. In 88 per cent, the hyperplasia was much reduced judging from what is seen in the untreated thyroid. In 6.7 per cent he believed the hyperplasia was increased.

Giordano[7] reports that in Basedow's patients who received iodin for one month, it was practically impossible to differentiate sections of the thyroid from a normal colloid gland.

No attempt will be made to discuss the changes in, or the relation of, the various ductless glands, except thymus, to hyperthyroidism. The very frequent presence of an enlarged thymus has raised the question of its possible relationship to hyperthyroidism. Warthin believes that hyperthyroidism only occurs in individuals with the so-called lymphatic constitution. A person, to develop this disease, must first have an enlarged thymus. He does not express an opinion in regard to the nature of this relationship.

Capelle[8] reports enlarged thymus in 95 per cent of hyperthyroidism dying following operation. Furthermore, 82 per cent of those dying directly from the disease and 44 per cent dying from inter-

current disease had enlarged thymus. Marine considers the enlarged thymus as secondary to the hyperthyroidism; part of a systemic reaction.

Garre reports a cure after thymectomy; and in Roentgen ray therapy of Basedow's the thymus region is treated and may be one factor in the beneficial results.

The pathologic physiology of hyperthyroidism is still highly speculative. No attempt will be made to present all the various hypotheses. Krehl believes that individual predisposition is a very important factor—the nature of this he does not attempt to explain. In support of this view, he mentions the inability to produce hyperthyroidism in every individual with simple goiter with either iodin or powdered thyroid.

Aschoff has a similar theory except that he considers this individual susceptibility as due to a hypersensitiveness of the nervous system. This, he believes, rather than an increase or abnormal secretion is responsible for the symptoms. He calls attention to the ease with which hyperthyroidism can be excited with dried thyroid, in an individual who has been cured by partial thyroidectomy. He believes there is more than one active principle and that a disturbance of balance in the relative amount of these may play a rôle.

Oswald advances the theory that the primary disturbance lies in the epithelial cells of the thyroid. No explanation is given for this cellular disturbance. The function of the epithelium is to remove the iodin from the blood and convert it into iodoglobulin so that it may be stored in the colloid; somewhat similar to the glycogenic function of the liver. Only iodin in this form is biologically active. He believes the epithelial cell has lost its power to convert iodin into a form where it can be stored; the iodin, consequently, is rapidly excreted from the body. This might account for the high iodin content of the blood in hyperthyroidism. The lack of storage ability leads to iodin deficiency. The reserve iodoglobulin disappears and with it the colloid. The compensatory hyperplasia is a response to inadequate thyroid secretion. This theory makes a strong appeal.

De Quervain leans toward multiple rather than a single active substance. Whether iodin is an important ingredient in all of them, he believes is an open question. He refers to Kendall's experiment where he obtained different physiological results with a substance soluble in acid from that obtained with a substance soluble in alkalies. He calls attention to the disassociation of the symptoms in cretinism, which he considers speaks for more than a single action substance. Here the gland is not always atrophied and at times the histologic structure suggests we are dealing with an active secreting tissue. The cardinal symptoms of cretinism are skeletal changes, intellectual defects and deaf-mutism. He states that in

cretins who are dwarfed, the thyroid is atrophied, while in those without skeletal defects the thyroid is at least normal in size and there is usually an obvious goiter. The genitalia and growth of hair are defective in the dwarfed cretin and not in the one of normal stature. Any explanation of the pathologic physiology must take into consideration the very small amount of thyroid tissue required for intense intoxication. This, apparently, discounts the view that we are dealing with a pure hypersecretion.

There is considerable confusion and inaccuracy in the current use of the term hypothyroidism. A patient with clinical myxedema or cretinism may be said to have hypothyroidism. Every patient, however, with a subnormal basal rate does not suffer from hypothyroidism. Perhaps in the future a clinical syndrome may be discovered which will enable us to detect a milder degree of thyroid deficiency than our present clinical myxedema. At present, however, clinical myxedema should be accepted as the criterion of hypothyroidism. Basal metabolism alone does not enable us to make such a diagnosis. We have at present under observation a lassie of 13 summers, with a goiter and a basal rate of −24. She is a normal alert individual. Another patient who about one and a half years ago had a subtotal thyroidectomy, now has a definite myxedema with a basal rate of −12.

The diagnosis of hyperthyroidism is not by any means always an easy task. The very slight enlargement of the gland in many instances and the great frequency of simple goiter, complicates the diagnosis. Most puzzling is that small but definite group where the signs and symptoms antedate an increase in the basal rate. There is another type, observed in individuals later in life and especially in long standing hyperthyroidism, where tachycardia or fibrillation is present but with a basal rate only slightly above the normal limit. These patients respond to iodin and the cardiac symptoms disappear permanently after subtotal thyroidectomy. This group can be easily overlooked and diagnosed as chronic heart disease.

Patients with goiter and hypertension may show an increased basal rate in the absence of hyperthyroidism. Here the temporary use of iodin may be of great assistance in determining the cause of the increased basal rate.

Occasionally we see a patient where after careful study we are in doubt as to whether we are dealing with a functional nervous disturbance or hyperthyroidism. I believe it is unwise to settle this question by subtotal thyroidectomy. Such a patient can well be kept under observation for a few weeks with frequent determinations of the basal rate, until such a time as we are satisfied with the diagnosis.

A considerable number of iodin hyperthyroidisms, either the direct result of iodin prescribed by the physician or from the use of iodized salt, have been observed during the past two years. Many of these

will return to normal after merely withdrawing the iodin. One such patient with a basal rate of +54 per cent, within six months had a subnormal rate with disappearance of symptoms. If one is certain of the cause, I believe that these patients—unless suffering from intense intoxication—can be wisely kept under observation for at least two months before advising radical treatment.

The purely medical treatment with the purpose of effecting a cure can be quickly dismissed. It is safe to say that drug therapy does not cure, although patients so treated may temporarily regain their health due probably to the tendency of this disease to spontaneous remissions. There is at present a widespread practice of looking on iodin as a curative agent. It cannot be too strongly emphasized that its chief field of usefulness is limited to preparing a patient for operative measures. Digitalis, I believe, is not indicated except in auricular fibrillation and here it fails to act in as satisfactory a way as in fibrillation of other origin. The best cardiac treatment is rest in bed.

The futility of physical and mental rest in the hope of effecting a cure has recently been demonstrated by Kessel and Hyman.[9]

We must conclude that there are only two forms of treatment that offer great hope of benefit or cure—surgery and Roentgen ray. I cannot at all agree with those who believe or at least state that Roentgen ray is valueless. After an experience extending over ten years, I am convinced that Roentgen ray is a valuable form of therapy and is free from certain undesirable complications as laryngeal paralysis, tetany and myxedema. Since the use of iodin as a pre-operative treatment, and lessened operative mortality, one of the arguments in favor of Roentgen ray has been removed.

What the internist awaits is the presentation by someone of satisfactory evidence of the percentage of cures by these two methods. By evidence, is meant the following of a series of cases treated by either of these methods for a period of five years. This follow-up cannot be done by a questionnaire which, at best, is a crude and unscientific method of obtaining therapeutic information. This is especially true of goiter, as shown by the character of the reports in the very limited series in the literature.

To obtain actual information, the previous patient must be examined by a competent physician both from the standpoint of clinical manifestations and basal metabolism. Such a method of follow-up requires much time and perhaps considerable expenditure of money. When we consider the very large sums spent on research—often with very meager returns—a problem of this character which must yield valuable information, and is true research, merits financial support. This matter has been emphasized because in my experience the results from surgery have not been as brilliant as we would expect from reading the literature.

Very recently a report has been made and to the best of my knowl-

edge, the only one in the literature, which fulfills these requirements, except that the period of observation is too brief to arrive at final conclusions. This is from the Lahey Clinic in Boston (Smith, Clute, Steider[19]). One hundred consecutive patients, operated upon at least one year previously were examined every three to four months by a competent clinician and at the same time the basal rate was determined. One patient died three months after operation; 92 were reported as having complete relief from their hyperthyroidism; the remaining 7 were definitely improved—were capable of doing a large part of their daily tasks, but still presented evidence of intoxication. The average basal rate of this group was +26.4 per cent; the highest +40 per cent; the lowest +7 per cent. Of the group free from symptoms of hyperthyroidism, 19 had a basal rate of −10 or more; 15 of these showed definite evidence of clinical myxedema and were taking thyroid extract or thyroxin. Even with the greatest care in regulating the dosage, they were unable to bring these patients to a normal functioning ability. They all show evidence of lack of endurance—fatiguing very easily. With further moderate increase in thyroid extract, they would develop symptoms of hyperthyroidism. It is true they were in much better condition to earn a livelihood than before the operation. It will be interesting to see if this entire group is followed, we may say for five years, whether more of these patients will develop myxedema. The lesson drawn from this report is that a treatment that effects a very high percentage of cures brings in its train a relatively high percentage of myxedema. This careful report is impressive as it indicates that much is still to be desired in the surgical treatment of hyperthyroidism.

If by treatment with Roentgen ray an equal per cent of recoveries can be shown, with lessened frequency of myxedema, then Roentgen ray would be the preferred method of treatment. For the purpose of comparison, we await with interest a report where equal care has been given to the follow-up Roentgen ray therapy.

During the many years in which a less radical removal was practiced, the permanent cures were probably in the neighborhood of 70 per cent. These results are comparable with what is accomplished with Roentgen ray. Postoperative myxedema was rare, at least in this country, and I have never seen a myxedema following Roentgen ray therapy, although they do occur. With the more radical procedures, the number of cures has reached approximately 90 per cent, although with the more prolonged follow-up this may prove to be too high, but there follows in the wake about 15 per cent of myxedema. It is not probable that Roentgen ray can duplicate this percentage of cures and if they did they would probably, just as in surgery, have a high percentage of myxedema. Fortunately or unfortunately, there is a limit to the amount of ray that can be used without injury to the skin and it is probable that the maximum

curative effect of Roentgen ray has been attained. Much as we may feel disappointed that higher percentage of cures goes hand in hand with an increase in myxedema, there is little question that this aftermath is less disabling than the original disease.

There is a rather large group of patients on whom I believe we are scarcely warranted in using Roentgen ray therapy. I refer especially to the severe types. As the beneficial results of Roentgen ray therapy rarely appear under eight weeks, it is a question whether such delay is warranted. A period of twelve weeks should elapse before we are at all certain Roentgen ray is not going to give results. In addition to the danger of increasing cardiac injury by this delay, there is also the financial loss from inability to work. It is, I believe, unwise in case no improvement appears after three months of treatment to discontinue the use of Roentgen ray.

In the milder types, where the patient is able to carry on at his work and where the probability of systemic damage from delay is light, Roentgen ray may be used. This, I believe, is a legitimate field for Roentgen ray therapy, as we are reluctant to submit such a patient to subtotal thyroidectomy with the danger of myxedema. We must also remember that this is the group with low surgical mortality. In any case, it is essential that even in the milder forms, prompt treatment by either surgery or Roentgen ray is vital, rather than trusting to chance for a spontaneous recovery.

The preparation of the patient for operation is a coöperative procedure followed by both physician and surgeon, who work together to determine the time when maximum improvement has developed. Plummer's discovery that iodin lessens toxicity and lowers operative mortality makes it desirable that the pre-operative iodin treatment is properly carried out. The much more palatable sodium iodid is just as efficient as Lugol's solution, which is converted into iodid after absorption. One cc. of Lugol's is equivalent to 150 mg. of sodium iodid. In case of persistent vomiting, the sodium iodid can be readily administered intravenously. It cannot be too strongly emphasized that the iodin is given only for the purpose of preparing the patient for surgery. If continued over a prolonged period, return of toxicity may occur and may fail to yield to further iodin therapy. It is also important that when iodin has been given it should not be discontinued until surgical measures have been carried out, as a violent relapse may result.

The question arises of continuing iodin after operation. The tendency at present is to continue its use for five or six weeks. Even in subtotal thyroidectomy, the small remaining tissue may become hyperplastic, with return of symptoms. Else[11] has recently advised that the long continued postoperative use of iodin will prevent recurrence. Clute and Lahey[12] report that the continued use of iodin does not prevent recurrence. This is in accord with our experience. It has been shown that if more than about two-thirds of the total

thyroid is removed in dogs, iodin will not prevent hyperplasia of the remaining portions. Apparently, this is also true in hyperthyroidism. Lahey, however, believes that very small doses of iodin are beneficial after the appearance of a recurrence.

Iodin is equally efficient in the hyperplastic and nodular type of goiter. This may be taken as evidence that the adenoma is not playing an active rôle in the intoxication.

The method of action of iodin is unknown. If the total capacity of the thyroid for iodin is less than 50 mg., the question arises as to why we should give such large doses. I believe it has not yet been actually determined that the massive doses, 1 cc. three times a day are essential or desirable. Certainly a large part of the iodin administered is never converted into the biologically active iodoglobulin, but is promptly eliminated from the body.

Much better remissions may be obtained if the patient is at rest during the iodin therapy. The length of time required to secure a satisfactory remission varies usually from eight to twelve days. Occasionally, a remission may be delayed and appear as late as three weeks. If the basal metabolism drops and then remains stationary for a few days, operation may be advisable even if the rate is still high. On the other hand, when little or no improvement is noted it may be advisable to continue the iodin for three weeks. Longer delay in hope of benefit is usually disappointing. About 5 to 10 per cent of patients fail to show an iodin remission.

The development of myxedema following any form of treatment is passed over rather lightly by some physicians. If recognized, it can usually be controlled if not entirely relieved. Lahey's experience, however, indicates that it is not a complication that can be lightly ignored. If the patient with this after effect falls into the hands of a physician who recognized the character of the trouble, well and good. Not all patients so afflicted will be so fortunate and failing to recognize the nature of their trouble may result in chronic invalidism.

There is little doubt that subtotal thyroidectomy is more successful in relieving hyperthyroidism than lobectomy. There may be, however, considerable difference of opinion as to whether every case should be submitted to this extreme procedure, with the possibility of acquiring myxedema. The less radical procedure followed for a quarter of a century is reported as curing 70 per cent of the patients, with very little of the danger of myxedema. Those not benefited could submit to a second operation, thus reducing the possibility of myxedema to this smaller group. Present experience suggests that there is a small group that can only be relieved of their intoxication by complete thyroidectomy. Here myxedema is unavoidable.

I believe it is unwise to be complacently satisfied with the present methods of treatment. Preventive measures should be further

investigated. Perhaps the physiologist and biochemist may soon solve the enigma of hyperthyroidism so that we may attack the cause rather than remove an organ which is possibly merely responding to some distant evil influence.

Conclusions. Our knowledge of the pathologic physiology of thyrotoxicosis is extremely limited.

In the present state of our knowledge, the term "thyrotoxicosis" is preferable to "hyperthyroidism." "Thyrotoxicosis with nodular goiter," is more accurate than "toxic adenoma."

We are greatly in need of accurate information about the end results of subtotal thyroidectomy. Such information cannot be obtained by a questionnaire. The patient must be carefully questioned and examined by a competent physician. As far as the writer has been able to determine, such a follow-up five years after operation has never been reported.

The present method of treatment may be the best that can be developed. It cannot, however, be considered highly satisfactory.

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A SIMPLIFIED METHOD OF GASTRIC ANALYSIS.

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In medical practice, the value of the analysis of the stomach contents has been much disputed. This is largely due to the fact that no simple and accurate test has been developed, and that the results obtained by the methods in general use have often not seemed of sufficient importance to warrant the time and labor necessary in carrying them out.

Many of the leading clinics of Europe have abandoned these methods and are using test-meal solutions to which an indicator has been added, thereby making possible accurate acid, volume and motility determinations. This work has largely been of an investi-

gative nature, and has recently been taken up by Bloomfield[1] in this country. Its application as a simple routine procedure in private and clinic practice would stimulate interest in gastric analysis and add materially to its dependability.

The test meals usually employed are of cereal foods, such as gruels, barley water and the well-known Ewald meal. The methods fall into 2 groups. In the first and most widely used, a single extraction of gastric contents is made at an interval after the introduction of the meal. In the second group extractions are made at intervals over a period varying from one and a half hours up to three hours. After the tube has been passed and the fasting contents removed, the test meal is given, which necessitates the removal of the tube in most cases as the patient may have difficulty in swallowing while it is in place. The tube is again passed and subsequent specimens collected. The technical disadvantages are that the tube often has to be passed twice, it frequently becomes clogged up with food particles, considerable saliva is swallowed, and an uncontrollable psychic stimulus is added to the direct stimulus to the gastric mucosa.

When we give an Ewald test meal, we not only introduce breadstuff into the stomach but between 400 and 500 cc. of water. Every sample of gastric contents extracted following the meal, so long as any of it remains in the stomach, will contain a mixture of gastric juice and of the meal in unknown proportions. Also it has been shown that the amount of toast given will neutralize surprisingly large amounts of hydrochloric acid. Consequently the acid value determined for any given sample of 10 cc. will be lowered by the unknown amount of water present and by the buffer action of the cereal. The extent of the reduction of the acid values will depend upon two factors. After the meal enters the stomach, it has the power of neutralizing the acidity up to a certain point but after this free acid will remain in the stomach contents. The time required for neutralization is quite unknown, and if part of the meal passes out of the stomach quickly, probably less neutralization takes place. A more important factor, however, is the rapidity with which the stomach empties. As the meal passes out, and the stomach mucosa continues to secrete, there is an ever shifting change in the relative proportions of meal and juice until the stimulus has left the stomach, and there is no accurate way of estimating the rate of emptying and the consequent diminishing dilution of the juice.

A modification of the methods of Lanz[2] and Bloomfield[1] is proving practical as a simple routine procedure in the investigation of patients complaining of gastrointestinal disorders. The meal consists of 50 cc. of 7 per cent alcohol containing 1 cc. of a 0.1 per cent solution of phenolphthalein in 95 per cent alcohol. It is prepared by adding 1 cc. of the indicator to exactly 49 cc. of the alcohol just before administering the meal, although the solution will keep

several weeks after it is made up. This is a 2 to 1000 solution of the indicator, and consequently dilutions of 50 per cent and greater can be read with the Dunning colorimeter which is already in general use for kidney function tests. This colorimeter is standardized for a 1 to 1000 solution, so that a reading must be divided by 2 in determining the percentage of phenolphthalein in a specimen for gastric analysis removed after introducing an alcohol-phthalein test meal. Specimens containing over 50 per cent of the meal are rarely encountered, and can be diluted down in order to read them. Doubling the concentration of the indicator makes the standard colorimetric readings but 2½ per cent apart instead of 5 per cent, and as a color shade may readily be seen to be between two standards, the error in the readings is only slightly over 1 per cent.

The technique of administering the meal is similar to that already in general use, except for the time at which the extractions are made. The patient should fast twelve hours, and be as quiet as possible during the test. A Jutte tube is passed and all the fasting contents is removed. This type of tube has proven far less disturbing to the patient than the Rehfuss tube with its larger perforated olive tip, and consequently minimizes psychic disturbances. The meal, warmed to body temperature, is introduced through the tube and two subsequent specimens are removed. For the first, 10 to 15 cc. are withdrawn twenty minutes after the meal, and the second is withdrawn forty minutes after the meal. All of the last specimen is removed and the total amount recorded. The specimens are tested for free hydrochloric acid immediately after their removal, and if achlorhydria is present the tube is not yet withdrawn. A solution of histamin representing 0.1 mg. per 10 kilos of body weight is injected subcutaneously. Gastric contents are removed thereafter until free hydrochloric acid appears or until three samples have been tested and found negative for free acid. A 1 to 1000 solution of histamin made up and sterilized by the autoclave for hypodermic use will keep at least a month.

The fasting contents and both the specimens removed after giving the meal are analyzed as in other methods of gastric analysis with the addition of the determination of the percentage of phenolphthalein present in Specimens I and II. They must be alkalinized with the minimum amount of 10 per cent sodium hydroxid in order to bring out the color, as an excess will cause them to fade out rapidly. These figures will represent the percentage of dilution of the gastric juice and also the exact proportion of gastric juice present in the second specimen. The true values may be obtained by means of a simple equation. The percentage of gastric juice present in a given specimen will be the difference between the percentage of phenolphthalein present and 100. One hundred over the percentage of gastric secretion present, times the titrated acid value will give the correct acid value for the pure juice. This may be readily deter-

mined from a graph. In this way, the percentage of dilution of the gastric secretion is easily calculated, which is not possible with any of the methods in general use. The gross characteristics of all the samples of juice are noted, the sediment from the fasting contents is examined microscopically, and the tests are carried out for occult blood, lactic acid and pepsin content as in the other types of analysis.

The alcohol-phthalein gastric test meal possesses many advantages, both in the technique of its administration and in making possible more accurate acid titrations and volume estimations. It is only necessary to pass the stomach tube once, as the alcohol is introduced through it into the stomach. This may be accomplished without the patient's knowledge thereby avoiding salivation and psychic gastric secretion. Samples of the stomach contents are readily removed, as there are no food particles to clog up the tube, and it is rarely necessary to filter them before analysis, as they are usually clear and colorless. The alcohol-phthalein solution has no buffer action on gastric acid, so there is no neutralization of acidity by the meal as with the cereal test breakfasts. It is a reliable and rapidly effective stimulus to gastric secretion.[3] The presence of the indicator, phenolphthalein, makes possible the determination of the number of cubic centimeters of pure juice present and of the acidity of the pure juice, and also the rate at which the stomach empties. This makes feasible the desirable brevity of the test as it is not necessary to wait two or more hours for the maximum acid value (the value of the pure or almost pure juice) to make its appearance, and there is an accurate forty minute volume reading which may be of considerable importance.

The use of histamin in cases showing no free acid in response to ordinary stimuli adds time and labor to the test, but, when carried out as outlined, saves doing a subsequent analysis following the injection of histamin. Two types of achlorhydria are now well recognized. The first is not a true one. There is no acid response to the presence of the usual test meals, but the mucosa is still able to produce acid if a powerful stimulant such as histamin is injected hypodermically. The second type is a true or complete achlorhydria and in these cases the mucosa has completely lost the capacity to secrete acid. This differentiation is of both therapeutic and diagnostic value.

There are certain unavoidable sources of error with this method as there are with the others. It is impossible to estimate the amount of alkaline mucus secreted by the gastric mucosa, but an excess may be identified upon inspection. The mucus that is swallowed is usually aërated. Taking precautions against swallowing the alkaline salivary secretions cannot be too strongly emphasized, as they may alter the acidity materially and interfere with the titrations. Gross blood will also reduce acidity, and no value can be attached to the free acid determinations in cases of actively bleeding

peptic ulcers or neoplasms. However, the chief source of difficulty is the regurgitation of the alkaline bile-containing duodenal contents in the stomach, which may actually produce a pseudoachlorhydria. The likelihood of such a regurgitation is greatly reduced if the patient is quiet and free from psychic disturbances. Anxiety or retching on the part of the patient during an extraction will often produce a gush of bile into the previously clear gastric contents. It has been suggested that uncontrollable regurgitation through the pylorus often occurs quite freely minimizing the value of gastric analysis.[4] It does occur, but usually carries bile with it to a lesser or greater degree, which is easily recognized and must be taken into account in judging results. Excess of bile has only been noted in 10 per cent of the cases, and then only in certain types of cases as a rule, notably neurotic individuals and those suffering from gall-bladder disease. As acid readings vary very little in repeated tests on the same subject, and as the clear specimens in a series of ten-minute extractions show no sudden drops in acid figures which regurgitation might well cause, it is difficult to believe that any material amount of regurgitation takes place clinically unless the tell-tale color of bile appears. If bile or blood is present in a sample, it is impossible to obtain an accurate phenolphthalein reading, but this has only occurred in both samples in 4 per cent in 150 cases. If bile does interfere with the analysis, the stomach may be washed out with water and the meal repeated with the probability that a second attempt will be successful, or else the test must be repeated on another day. Because bile appears at one trial, does not necessarily mean that it will appear at another. These disadvantages actually interfere with the results in only a very small number of cases.

There is a small group of cases in which the series of acid readings seem quite incompatible. The technique and results should be carefully scrutinized before the method of analysis is judged unreliable, because the normal and pathological physiology of the stomach vary surprisingly. There are cases which may show normal or even high acid figures in the fasting contents, and no free acid after the meal. Such a finding may be due to excess bile or mucus, but in rare instances is undoubtedly due to an open pylorus through which practically all the meal passes quickly, producing little or no stimulus to acid secretion. Occasionally there is a marked difference in the titratable acidity of the two specimens, which, if alkalinizing factors are eliminated, may represent a quick response to the stimulus with early emptying of the stomach, or a slow response and considerable gastric mucus.

Probably no test of gastric function which gives the maximum degree of information will ever prove sufficiently simple and brief to be applicable to routine clinical use. However, this forty-minute test has proven entirely adequate except in a very occasional case,

and deserves a thorough trial as a readily applied adjunct to ordinary diagnostic procedures.

Summary. 1. The methods of gastric analysis in general use give very unreliable acid and volume determinations and offer many technical difficulties.

2. The use of alcohol as a meal provides an adequate stimulus to gastric secretion and eliminates many technical difficulties.

3. The Jutte tube is more readily passed and causes less psychic disturbance than the Rehfuss tube.

4. The addition to the meal of an indicator such as phenolphthalein in known concentration makes possible the determination of the acidity of the pure juice and of the exact emptying time.

5. The Dunning colorimeter, which is in general use for renal function tests, can also be used for the alcohol-phthalein test meal.

6. The exact volume of juice present forty minutes after administering the meal can be calculated.

7. The use of histamin in cases of suspected achlorhydria is incorporated into the test.

8. The alcohol-phthalein test meal takes only forty minutes to produce the essential information in nearly every case.

9. The test is sufficiently simple and accurate so that gastric analysis should be more generally and effectually carried out.

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CLINICALLY PRIMARY TUBERCULOUS PERICARDITIS.

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Tuberculous pericarditis has engaged the interest of clinicians and pathologists for various reasons—among others in a discussion over the possibility of its primary or secondary character.

That tuberculosis can occur in the pericardium and nowhere else in the body, seems to be established. Hedblom[5] collected 13 cases and Rawls[10] has since added another. Riesman[2] calls attention to the "clinically primary" type by which he means that active tuberculous lesions elsewhere in the body cannot be demonstrated at the onset of symptoms. Careful search in the literature has revealed only 11 such cases, in which the diagnosis cannot be ques-

tioned and in which the clinical history is given in enough detail to draw comparisons. In addition to these, 2 others are being added, both being on the same service at the Philadelphia General Hospital at the same time.

Case Reports.—CASE I. O. M., a male negro, aged twenty years, was admitted to Dr. Schnabel's service September 20, 1926, with a temperature of 102° F., pulse rate of 80 and respirations of 25 per minute, complaining of shortness of breath and pain in the epigastrium.

His parents were both dead of unknown causes. He had had one Neisserian infection, but no other illnesses that he could remember.

The history of his present illness is indefinite. He had quit work as a laborer in an iron yard three months before admission, because of weakness. There had been intermittent and mild pain in the epigastrium and at the time of the pain he would be short of breath. There had been some cough with a little expectoration and an occasional night sweat.

Physical examination showed an apathetic negro, breathing rapidly with marked working of the alæ nasæ. The chest gave a flat percussion note posteriorly from the fifth rib downward on both sides. Cardiac dullness was increased and was continuous with the pleural dullness. The heart sounds were muffled and no murmur or friction rub was heard. The pulse diminished in force during inspiration (pulsus parodoxus). The liver was enlarged and tender and there was some ascites.

Two days after admission, 540 cc. of clear fluid were removed from the left, and 1000 cc. from the right pleural cavity. In the next two days, 175 cc. and 1000 cc. of bloody fluid were removed from the pericardium. Following this, the pulsus paradoxus disappeared and a pericardial friction rub was heard for the first time.

There were 4,400,000 erythrocytes and 6700 leukocytes per c.mm. The urine showed a small amount of albumin and an occasional cast. Cultures of the blood, pleural and pericardial fluids were sterile. By staining methods, no tubercle bacilli were found in the sputum, nor in the sediment of the fluids removed from the pleura or pericardium. The Wassermann reaction was negative.

The Roentgen rays showed a much enlarged cardiac shadow and fluid in both pleural cavities. Neither in the pictures taken on admission nor in those taken subsequently was there any evidence of pulmonary tuberculosis.

Fever was present during his entire stay in the hospital. The highest recorded temperature was 103° F., and for the first six weeks of his stay it varied between this and 101° F. The first normal temperature was recorded six weeks after admission. During the next three months, there was a mild fever each day, the temperature rising to 100° or 101° F. The fluid in the pericardium increased in quantity and was only partially removed by thoracentesis. There were many times when this procedure failed, probably because the needle became plugged with fibrin shreds which were always present in the fluid. Dyspnea and edema, due to cardiac failure, varied with the success of the tappings. At one time the face, left breast and arms were very edematous.

During February and March, there was gradual improvement until he was able to be up and around the ward all day without discomfort, despite the fact that the cardiac dullness was still much greater than normal, and the temperature was between 99° and 100° F. He was discharged March 25, disappeared immediately and has not been heard from since.

Fluid removed from the pericardial sac on November 14 was injected into a guinea-pig. A necropsy on this pig on December 30 showed typical tuberculosis.

ANALYSIS OF CASES.

Case.	Sex and age.	Race.	Initial symptom.	Diagnosis based on.	Duration, mos.	Termination.	Highest fever.	Edema	Dyspnea	Cough.	Fluid removed,* cc.			Necropsy findings.
											Pericardium.	R. pleura.	L. pleura.	
Case I (O. M.)	M. 20	Negro	Pain in abdomen	Guinea-pig inoculation	9	Improvement; went home	103.0° F.	+	+	+	1255	1020	540	Tuberculous pericarditis; miliary tuberculosis; tuberculosis of mediastinal glands.
Case II (C. A.)	M. 22	Negro	Cold	Guinea-pig inoculation	4½	Death	105.0° F.	+	0	+	2100	1100	700	Pericardium adherent; miliary tuberculosis.
Osler[1]	M. 52	White	Cough	Postmortem	5	Death	102.0° F.	+	+	+	0	0	0	Tuberculous pericarditis; miliary tuberculosis.
Osler[1]	F. 39	Negro	Dyspnea	Postmortem	5½	Death	103.0° F.	+	+	+	300	0	0	
Hedblom[5]	M. 36	White	Sore throat	Guinea-pig inoculation	15	Improvement; went home	101.0° F.	+	+	+	6500	0	700	Pericardium adherent; right pleura adherent; healed tuberculosis of right upper lobe.
Riesman[2]	M. 32	White	Pain in shoulders	Guinea-pig inoculation	5	Death	101.0° F.	+	+	+	0	0	2850	
Amaudrat[9]	M. 13	White	Dyspnea	Guinea-pig inoculation	6	Cured	103.5° F.	+	+	0	300	0	+	
Masselot[8]	M. 30	Negro	Pain in chest	Postmortem	9	Death	?	+	+	*	200	0	0	Tuberculous pericarditis; miliary tuberculosis (liver); tuberculosis of mediastinal lymph nodes; large caseous mass, hilum right lung; right apex clear.
Jauch[7]	M. 23	White	Fever	Postmortem	3	Death	103.6° F.	0	0	0	480	—600—		Tuberculous pericarditis; miliary tuberculosis.
Ehrenclov[6]	M. 18	White	Severe cold	T. B. C. stained in fluid	4½	Improvement; left hospital; later died	104.0° F.	+	+	+	300	0	750	Not obtained.
Rawls[10]	M. 51	Negro	Dyspnea	Guinea-pig inoculation	4	Death	?	+	+	+	1000	0	0	Tuberculous pericarditis; died after artificial pneumopericardium.
Dillon[11]	M. 19	Negro	Dyspnea	Postmortem	5	Death	103.0° F.	+	+	0	0	0	0	Pericardium adherent; tuberculosis of spine; tuberculous endocarditis; miliary tuberculosis.
Renaud[12]	F. 55	White	Grippe	Postmortem	22	Death	"Slight"	+	+	0	0	0	0	Pericardium adherent; healed tuberculosis apices of lungs; arthritis.

*Figures include both antemortem and postmortem removals.

CASE II.—C. A., a male negro aged twenty-two years, was admitted November 12, 1926, with a temperature of 102° F., pulse rate of 130 and respiration of 35 per minute, complaining of pain in the right chest.

His mother died of an unknown cause when he was eight years of age, and he knew nothing of his father. He had had smallpox in childhood and no sicknesses since, until his present trouble. This started with a "cold" and cough six weeks before admission. He stayed away from work as a laborer for four weeks, worked only one week when he caught another "cold" and then came to the hospital. The pain in the chest was not severe. He had had a cough and spat a little blood at one time. Two days before admission his feet had been swollen.

Physical examination showed a well-nourished young negro, lying flat in bed. He was coöperative and in no discomfort. There was evidence of some fluid in the right chest. Otherwise the lungs were normal. The cardiac dullness extended from the right nipple to the left anterior axillary line. The heart sounds were distinct, and neither murmur nor friction rub was audible. The liver could be percussed one finger's breadth below the costal margin. There was no ascites. There were two crusts on the left elbow, apparently the result of a slight abrasion.

After 700 cc. of bloody fluid were removed from the pericardium, a typical to-and-fro friction rub was audible over the body of the heart. The blood count was 3,980,000 erythrocytes and 6000 leukocytes to the c.mm. The urine had a specific gravity of 1.008 and neither sugar nor albumin were present. The Wassermann reaction was negative. There were no tubercle bacilli in the stained smear from either the sputum or the sediment of the pericardial fluid. A guinea-pig inoculated with this fluid showed tuberculosis when necropsied five weeks later.

On admission, the Roentgen ray picture showed a tremendously enlarged cardiac shadow, the left border being shown in the axilla. This and three subsequent pictures showed no evidence of pulmonary tuberculosis.

The same difficulties in withdrawing fluid were encountered in this man as in the other patient. The fluid, however, did not cause as much embarrassment to the circulation. There was decided improvement and for awhile he was able to be up and around the ward in a wheel chair. On December 29, six weeks after admission, a Roentgen ray picture showed a mottled shadow in the left upper lobe. Each subsequent picture showed more involvement of the lung tissue until, in the last picture taken February 6, it was impossible to see the outline of the heart. He became weak and lost weight rapidly during January and died February 13.

Fever was present until two weeks before death. It was of a type similar to that seen in Case I. However, the temperature was lower during the first six weeks although there was one reading of 105°. Soon after the first signs of pulmonary tuberculosis were found in the Roentgen ray picture, there was a period of greater fever, followed by gradual defervescence. During the last two weeks of life, the temperature was normal, probably due to weakness.

Necropsy. Miliary tuberculosis of the lungs, spleen, liver, adrenals, lymph glands and kidneys. This was farthest advanced in the spleen and lymph glands, where the normal tissue was almost entirely replaced by caseation.

The tubercles varied in size in the different organs. In the lungs they were the size of a dime, in the liver the size of a pinhead, while in the kidney they were microscopic. The pericardium contained 1000 cc. of bloody fluid. Both layers of the pericardium were thickened and covered with an exudate 2 to 3 mm. thick. There were no adhesions. The heart muscle was only slightly hypertrophied and the valves were normal. There were 600 cc. of clear fluid in the right pleural cavity and 900 cc. in the abdominal cavity.

Comment. These 2 cases and 11 from the literature are grouped together in the accompanying table. From this it will be seen that the outstanding features of this disease are cardiac failure with fever and great increase of the cardiac outline, with few or no symptoms referable to the chest. The onset is very insidious, the enlarged heart area being easily demonstrable when the person appears for treatment. The duration of the disease is long, the shortest case lasting three and the longest twenty-two months after apparent onset. It is not necessarily fatal. Of these 13 patients, 9 died, 1 made a complete recovery and 3 were discharged much improved, but with the heart still abnormal. (One of these subsequently died of a "relapse.") Of those that died, 2 showed decided improvement in the heart condition but later developed miliary tuberculosis, so that in 6 out of 13 there was a successful attempt at an arrest of the pericardial tuberculosis.

There were 11 men and 2 women, 6 negroes and 7 whites. Of the American cases, 5 were negroes and 4 were whites. The youngest was thirteen and the oldest fifty-five years of age. Shortness of breath was the symptom most constantly found, being present in all but 2, and 1 of these 2 had a respiratory rate of 35 per minute without discomfort. Cough and weakness were almost as constant. Pain was uncommon and occurred in only 3. It was located by one in the shoulders, by another in the chest and 1 had pain in the belly, probably from the liver. The leukocyte count was given in 4, the highest being 13,000 and the lowest 6000. Fever was a prominent symptom in all. There was no characteristic type or variation but in all in whom figures were available, it was 101° F. or over and in 6 it was 103° F. or over. Edema was present in 11 and edema of the face was especially mentioned in 3. Pleural effusion was present in 7, the left pleura being involved six times. The left was involved without the right four times. Ascites was present in 5. Fluid in all four serous cavities in our first case made us think that we were dealing with a polyserositis. However, the different character of the fluids soon corrected our error, that from the pericardium being bloody, while from the other cavities it was clear straw-colored. As in Riesman's case, the pleura may be involved in the same process as the pericardium.

From the pericardium, fluid was removed during life in 7 and was found postmortem in 2 others. In 4 (all autopsied) the pericardium was adherent. The fluid was bloody in all but 2, where it was "turbid" and "purulent." In 1, it coagulated on standing. The quantity of the effusion varied greatly, 50 to 2500 cc. being removed at a single tapping. Of the 4 who lived to leave the hospital, all had had fluid removed from the pericardium.

The diagnosis was proven from antemortem materials in 7. In only 1 case[6] was it possible to demonstrate the tubercle bacillus in the pericardial exudate by staining methods. In the other 6, the

diagnosis was made by guinea-pig inoculation with fluid from either the pericardium or pleura. The guinea-pig test sometimes failed to show tubercle bacilli on the first inoculation, so that repeated tests should be made with different samples of fluid.

There were 9 necropsies. Miliary tuberculosis was present in 6. Chronic tuberculosis of the lungs was present in 3 but in 2 of them it was slight and considered inactive. In 4 others, the failure to find chronic pulmonary tuberculosis was commented upon. In Masselot's[8] case the right lung was infiltrated by tuberculosis from the mediastinum outward, the apex being healthy. Caseous lymph glands in the mediastinum are mentioned in only 3 instances. Bone tuberculosis was present in 2. In 1,[12] there was a remarkable arthropathy of many joints, resembling that seen in chronic lung suppuration. The pericardium was greatly thickened, in some 1 cm. or more. There were no valvular lesions, and in only 1[11] had the tuberculosis extended to the endocardium. All 3 who died without the miliary form of the disease had marked evidence of cardiac failure. In 2 of these, the pericardium was adherent and the third died eight hours after a pericardial aspiration and artificial pneumopericardium.[10] Considering the very large amounts of fluid which were tolerated in the pericardium (2500 cc. in Hedblom's case), it would seem that the danger of death from cardiac failure is not great, particularly in those with fluid. In 1 of Osler's cases, there was decided improvement in the general condition with a real gain in weight and yet at autopsy the pericardium was adherent. (The cause of death was miliary tuberculosis.)

Since we know, as a result of the guinea-pig inoculations, that tubercle bacilli are fairly numerous in the pericardial fluid, and since the incidence of miliary tuberculosis is much greater in pericardial tuberculosis than in tuberculosis elsewhere in the body, it is reasonable to presume that some of the infected fluid may return to the circulation. For this reason and for the comfort of the patient, it seems essential to remove the fluid. Paracentesis is not as easy as in other forms of pericarditis because of the thickened, necrotic condition of the membrane, floating fibrin shreds, and the thick consistency of the fluid itself, which may clot. There were many dry taps in the 2 cases here reported. When tapping fails, one should consider pericardotomy. In the above mentioned Case II, which ended fatally, we were under the impression, gained by repeated taps, either dry or yielding only small amounts of fluid, that the enlargement of the cardiac outline was due to hypertrophy and yet at necropsy 1000 cc. of fluid were found in the pericardium. Had a pericardotomy been done, it is conceivable that the bacilli would not have been forced into the circulation producing the miliary tuberculosis from which he died. Dyspnea is not a reliable guide to the amount of fluid present, as this man was at no time uncomfortable.

Tuberculosis should be suspected in every case of pericardial effusion, the more so if it is purulent or bloody. In the absence of fluid, cardiac decompensation with increase in the cardiac measurements and accompanied by decided fever over a long period, should cause tuberculosis to be suspected.

Summary. Death occurs in tuberculosis of the pericardium from either heart failure or miliary tuberculosis, the latter being the more common.

Miliary tuberculosis is much more frequent in this than in other forms of tuberculosis.

In most cases, fluid is present in the pericardial sac and this fluid contains viable tubercle bacilli.

This fluid should be evacuated frequently. When it is impossible to do this by paracentesis, a pericardotomy should be done.

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REVIEWS.

DISEASES OF THE GALL BLADDER AND BILE DUCTS. By EVARTS AMBROSE GRAHAM, A.B., M.D., Professor of Surgery, Washington University School of Medicine, St. Louis, etc.; WARREN HENRY COLE, B.S., M.D., Instructor in Surgery, Washington University School of Medicine, etc.; GLOVER H. COPHER, A.B., M.D., Assistant Professor of Surgery, Washington University School of Medicine, etc.; and SHERWOOD MOORE, M.D., Professor of Radiology, Washington University School of Medicine, etc. Pp. 447; 224 engravings and 8 colored plates. Philadelphia: Lea & Febiger, 1928. Price, $8.00.

THIS book accomplishes two most desirable things: (1) It brings together in the English language, for the first time since Rolleston's "Diseases of the Liver, Gall Bladder and Bile Ducts," a digest of all the important knowledge regarding the human biliary system and (2) it summarizes, from the standpoint of its originators, the work thus far done in connection with cholecystography.

An enormous amount of research, stimulated to a large extent by Lyon's development of a technique for nonsurgical biliary drainage and Graham's own work on the roentgenologic study of the gall bladder, has been in process during the past decade. This has revolutionized many of our ideas regarding the physiology of the biliary tract and has put others on a firmer foundation. All of this work is covered in the treatise, and is given, in the reviewer's opinion, its due emphasis. For those interested in the original material in the literature the book will be found invaluable, since it gives complete references, as is most convenient, at the foot of each page. When controversial matter is encountered the authors' tendency has been to state the various opinions and the grounds on which they are based rather than to emphasize their own.

Cholecystography occupies the largest section of the book (106 pages) and under this heading are included its historical development, its technique and a full discussion of its diagnostic efficiency. A chapter is devoted to the tests of hepatic function and the final one to the surgical treatment of cholecystitis. This book will appeal to the internist, the surgeon, the roentgenologist and the laboratory worker alike. T. M.

SERUM DIAGNOSIS BY COMPLEMENT FIXATION. By JOHN A. KOLMER, M.D., DR.P.H., D.Sc., LL.D., Professor of Pathology and Bacteriology in the Graduate School of Medicine of the University of Pennsylvania and Member of the Research Institute of Cutaneous Medicine. Pp. 583; 65 engravings. Philadelphia: Lea & Febiger, 1928. Price, $7.00.

THIS is essentially a summary of the clinical and laboratory investigations made by the author in serum diagnosis by complement fixation, not only in syphilis but likewise in the field of the bacterial, protozoal and metazoal diseases of human beings and the lower animals. These methods are also applied to the identification of blood and seminal stains, the detection of meat and milk adulterations and other soluble albumins. New methods are discussed along with practical applications, including numerous references to the investigations of other laboratory workers.

In Part I are stated the important principles of serum hemolysis and complement fixation. Part II deals with the principles of technique. In Part III is presented the technique of the author's methods in detail, while Part IV is devoted to an account of the sensitiveness, specificity and practical applications of methods in serum diagnosis and treatment of various diseases.

This work is to be recommended not only to serologists and laboratory technicians but also to practising physicians and veterinarians.

W. K.

GONOCOCCAL URETHRITIS IN THE MALE. FOR PRACTITIONERS. By P. S. Pelouze, M.D., Associate in Urology and Assistant Genito-urinary Surgeon, University of Pennsylvania; Fellow of the Philadelphia College of Surgeons. Pp. 357; 78 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $5.00.

ONE would like to see this book in the hands of every young man whose practice of medicine is going to cover the treatment of gonorrhea in the male, for much of the fundamental information contained herein is entirely unknown to the practitioner. The volume is divided into two parts. In the first 246 pages the principles underlying the diagnosis and treatment of disease are fully discussed. Part II consists of 48 cases illustrative of various types of infection. The first chapters (Applied Anatomy, Normal Histology, The Gonococcus, Pathology, Immunity, The Influence of Cell Type Upon Gonorrhea, Defensive Processes Against Gonorrhea) represent a logical, lucid theory of what urethral gonorrhea is, evidently based upon long experience in the clinic, in the laboratory and in the classroom.

Consider, for example, the admirable brevity of the following statements: "(1) Gonorrhea is a disease due to tissue penetration by the gonococcus. (2) The germs reach points that we admittedly do not reach without germicidal substances. (3) The deeper-lying bacteria outlast the stage of exudation, and are not greatly affected by the process of phagocytosis. (4) Under ideal conditions recovery may occur without any treatment whatever."

And the following: "1. The susceptibility to and tenacity of gonorrheal infection of the urogenital tissues bear a direct relation to the height of the superficial cells. The flatter the superficial cells, the harder they are to infect, and the more readily do they recover if infected.

"2. Stratification of cells is definitely protective. The fewer the strata of susceptible cells, the deeper is the gonococcal penetration and the greater and more prolonged is the inflammatory action.

"3. The susceptibility of transitional epithelium bears an inverse relation to the dilatability of the structure it covers. . . .

"4. Long mucous channels of small caliber, though lined with the most susceptible types of cells, rarely will become infected through continuity of surface.

"5. The tenacity of infection in all types of mucosæ bears a direct relation to the drainage possibilities of the surface involved.

"6. If absolutely and permanently blocked a small mucous crypt eventually will accomplish its own sterilization. In other words, to retain virulent infection for great periods such crypts must be able to empty themselves from time to time."

The author has introduced a chart system of studying the progress of the disease which must be a great assistance in teaching to students the reactions of the urethra to sexual, alcoholic or therapeutic traumata. He uses his charts to illustrate how the trauma of the treatment excites exacerbations of infection.

"As physicians it is probable that we seldom realize how much our therapeutic efforts commonly do toward prolonging instead of shortening this battle. Many of our forms of treatment are definitely devitalizing to an urethral mucosa that is crying for real help, and instead of helping we often hinder.

"At least 95 per cent of male gonorrheics in this country are being treated by the general practitioner. The vast majority of physicians will admit frankly that they really know little about the disease. This need not hurt their feelings very much because so many of the urologists are interested in surgery, and are not thinking gonorrhea, and do almost as many foolish things and call them 'treatment.' Our textbooks contradict themselves and one another, and in doing so they spread confusion. . . . If we love humanity this places upon us as humanity's physicians the necessity of getting very busy and finding out how to treat gonorrhea before the world crumbles from advanced age. . . .

"We should be in a position to see how hopelessly ridiculous are the claims of the manufacturers of gonococcicides, based upon their action in the laboratory where conditions in no way resemble those in the urethral mucosa. . . .

"The first, the so-called oral plan of treatment, throws upon the patient and his reactive processes the entire task of curing the disease. . . .

"The second plan of treatment is unquestionably based upon the idea of slaying bacteria through direct local attack by some germicidal substance. It does not take into account any reactive powers the patient may be able to marshal, but winnows the chemical products of the world in the more or less vain hope of finding an ideal germicide.

"There is more evidence to suggest that both are wrong than that either is wholly right."

These quotations illustrate the vehemence of the author's opinions. He endeavors to justify the methods of treatment of which he approves in the following chapter in which he repeatedly condemns astringents but says: "The best single chemical that we now use is potassium permanganate in proper strength solution."

We shall not disclose the plot of the story further. It is impracticable to condense it.

Inasmuch as the author boldly pronounces himself at odds with all the prevailing methods of treatment, it would be vain to pick out items in his therapeutics which do not happen to appeal to the reviewer. In the main, we can agree with the author far more generously than he seems willing to do. His principles of treatment are undoubtedly right. But his objection to astringents, coupled with his devotion to potassium permanganate, forms a noteworthy conjunction. It is interesting to see that he no longer insists upon the close connection of cysts about the bladder neck with tuberculosis elsewhere in the body.

This treatise is healthy, original, vigorous. We can wish that it were not quite so personal. E. L. K.

RENÉ THÉOPHILE HYACINTHE LAENNEC. A MEMOIR. BY GERALD B. WEBB, M.D., President, Colorado School of Tuberculosis. Pp. 146; 13 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $2.00.

AMONG the biographical reprints from the Annals of Medical History none is happier than this centenarial sketch of Laennec, "greatest of physicians." Though perhaps some may hesitate to grant him this proud eminence, none can deny that the young Frenchman's figure is one of the most compelling in the history of

medicine. In this brief story of a short but brilliant life, bits of the biographer's philosophy crop charmingly out: "The father of Laennec was a person of excellent physique and sound health, consequently of a winning and joyous nature," but further on "this later Polonius" appears "with his infinite capacity for the unseasonable;" comparing Broussais to Laennec: "one fought passionately for an error, the other dispassionately for the truth." E. K.

RECENT ADVANCES IN CHEMISTRY IN RELATION TO MEDICAL PRACTICE. By W. MCKIM MARRIOTT, B.S., M.D. Pp. 141. St. Louis: C. V. Mosby Company, 1928. Price, $2.50.

THIS little book is a printing of the 1927 Series of Lectures before the San Diego Academy of Medicine. It is an attempt to sketch in a most elementary way some of the important bearings of chemistry upon body function in health and disease. It may serve to call the reader's attention to some of these applications of chemical theory and method. However, the absence of a bibliography prevents its serving as a guide to more detailed presentations. It indicates correctly the fragmentary character of the development of this field of knowledge, but it hardly serves to suggest to the reader how much, even now, thorough study of any part of this general field will reveal. J. A.

THE DETERMINATION OF HYDROGEN IONS. By W. MANSFIELD CLARK. Third edition. Pp. 717; 100 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $6.50.

FOR many years among the most valuable books in our laboratories of biological chemistry have been the earlier editions of this book. The extensions and additions in this new third edition are so fundamental as to make it essentially a new work. The author now includes a treatment of the theory of hydrogen ion in terms of the activity concept. His presentation of the thermodynamics necessary to grasp the concepts of free energy and activity are almost unique in their comparative simplicity and clearness. His chapter on the theory of Debye and Hueckel is the best introduction in English to this theory with which the reviewer is familiar. His discussion of temperature coefficients will clear for many a most obscure phase of the field.

He has made his book an introduction into the theory of solutions at a time when a grasp of this theory has become indispensable to the worker in biological chemistry, and he has used the new concepts

to give a sounder significance to pH. His new treatment of the bibliography will prove an invaluable guide for the worker entering any unfamiliar field in the application of pH methods. Finally, the book is written with a literary style of distinct charm and is permeated with a philosophy of science which will carry the reader on from page to page unwilling to postpone at least a glimpse of its treasures. J. A.

ADDRESSES ON SURGICAL SUBJECTS. By SIR BERKELEY MOYNIHAN, (BART.), President of the Royal College of Surgeons of England. Pp. 348; illustrated. Philadelphia: W. B. Saunders Company, 1928. Price, $6.00.

THE author of this most interesting collection of essays needs no introduction to the profession. These various contributions have been presented to the public previously, but having them bound in one volume is a distinct advantage. The book needs no critical review. It merely requires the calling of the attention of the profession to the fact that it is published. Its merits justify its popularity. E. E.

BOOKS RECEIVED.

New Books.

Third Report of the Commission on Medical Education, October, 1928. Pp. 70. Willard C. Rappleye, 215 Whitney Avenue, New Haven, Conn., Director of Study.
A sane and thoughtful presentation well worth the perusal of all who are interested in medical education. Copies will be supplied gratis by the Director of Study.

Problems in Surgery. University of Washington Graduate Medical Lectures for 1927.* By GEORGE W. CRILE, M.D. Pp. 171; 49 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $4.00.

Le Nefrosi. By ALESSANDRO ESPOSITO. Pp. 212. Milan: Societa Anonima Instituto Editoriale Scientifico, 1928.
Written to fulfil the need of a comprehensive review of the nephroses in the light of modern European and American studies.

*Modern X-ray Technic.** By ED. C. JERMAN. Pp. 260; illustrated. St. Paul; Minnesota; Bruce Publishing Company, 1928.

*A History of Pathology.** By ESMOND R. LONG, PH.D., M.D. Pp. 291; 55 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $5.00.

* Reviews of titles followed by an asterisk will appear in a later number.

Neurological Examination. *By CHARLES A. MCKENDREE, M.D. Pp. 280; 88 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $3.25.

*A Textbook of Pharmacology and Therapeutics.** By HUGH A. MCGUIGAN, M.D. Pp. 660; 43 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $6.00.

Medical Clinics of North America. (New York number—November, 1928.) Pp. 334; 64 illustrations. Philadelphia: W. B. Saunders Company, 1928.

Medical Record Visiting List or Physicians Diary for 1929. New York: William Wood & Co., 1929. Price, $2.00.

*Total X Fotos.** By DE DENIS MULDER. Pp. 57; 38 illustrations. The Hague, Holland; G. C. T. Van Dorp & Co., 1928. Price, $1.80.

Practical Poultry Management. By JAMES E. RICE, B.S. in Agr. and HAROLD E. BOTSFORD, B.S. Pp. 506; 307 illustrations. New York: John Wiley and Sons, Inc., 1928. Price, $2.75.

*Idiosyncrasies.** By SIR HUMPHRY ROLLESTON, BART., K.C.B., F.R.C.P. Pp. 119. London: Kegan Paul, Trench, Trubner & Co., Ltd., 1928.

New Editions.

*Textbook of Pharmacology and Therapeutics.** By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S. Pp. 743; 73 illustrations. Ninth edition. Philadelphia: Lea & Febiger, 1928. Price, $6.00.

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN, M.D., M.A. Fourth edition. Pp. 998; 38 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $9.00.

This continues to be the most important work on the subject that we know of and truly indispensable to anyone treating diabetic patients.

Regional Anesthesia. By GASTON LABAT, M.D. Second edition. Pp. 567; 367 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $7.50.

Clinical Electrocardiography. By SIR THOMAS LEWIS, M.D., F.R.S., D.Sc. Pp. 128; 107 illustrations. Fourth edition. London: Shaw and Sons, Ltd., 1928. Price, 8s. 6d.

With the steadily increasing number of electrocardiographs in use, this booklet becomes of increasing value. As a supplement to the Clinical Disorders of the Heart Beat by the same author, it is invaluable to student and internist.

The Elements of the Science of Nutrition. By GRAHAM LUSK, PH.D., SC.D. Fourth edition. Pp. 844. Philadelphia: W. B. Saunders Company, 1928. Price, $7.00.

Like virtuosos of song, the author makes another final bow after an interval of eleven years. As in the past, this book fulfills its aim "to review the scientific substratum upon which rests present-day knowledge of nutrition."

The Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN, M.D., F.R.C.P. Fourth edition. Pp. 209. New York: Paul B. Hoeber, Inc., 1928. Price, $2.50.

The present revised and enlarged edition continues to be the best brief book upon this subject with which the reviewer is familiar.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

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AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Nomenclature of the Accessory Food Factors.—In 1913 Funk applied the term *vitamin* to a group of nutrient principles. Etymologically at this time the term was correct, as it was believed that the substances were chemically allied to the amines and that they were something connected with life processes. Subsequent studies have not borne out this belief as to amine derivatives, yet the term *vitamin* has persisted, spelled, however, without the "e" and indicating so far as an "amin" is concerned, nothing. As new vitamins were described, they were classified largely on the basis of their solubility and from a historical standpoint letters were assigned to these vitamins according to the sequence of their discovery. JONES (*Science*, 1928, **68**, 480) contends that the term vitamin was incorrect to start with and that with a subdivision of certain of the vitamins, namely vitamin B, into different fractions, it is necessary to have a new nomenclature for these accessory food factors. He suggests that the group name be *advitant*, indicating the close association of the substances with life processes. A provisional name could be given, with the suffix *amin* retained, indicating the disease of which it is preventive. Thus vitamin D would be called *rachitamin* as a provisional name. When the chemical composition is known it could be called *rachitasterol*. In place of vitamin A or fat-soluble A, the provisional name should be *ophthalamin*. The permanent name would not be given until the composition of the unknown substance was definitely known. This suggestion of the author is well worth employing in medical terminology. It would save considerable confusion and at the same time be definitely indicative of just what the particular advitant prevented.

Recent Cases of Undulant Fever in New York State.—The increase in the number of cases of undulant fever, notably in the South, has been recognized by numerous physicians. As a matter of fact, the United States Public Health Service, in a recent bulletin, has gone so far as to say that in rural communities undulant fever will soon be more important from a public health point of view than typhoid fever. As evidence of this increased recognition of the disease, whether caused by the Brucella abortus or Brucella melitensis, is a report by GILBERT and COLEMAN (*J. Infect. Dis.*, 1928, **43**, 273) of some blood examinations made in New York State on a series of cases occurring in that community. The authors examined 213 blood specimens of individuals who had continued fever which gave no reation to Bacillus typhosus. Sixteen of these were found to give positive agglutination reactions with organisms of the abortus-melitensis group. Of 19 blood specimens which were to be examined for evidence of undulant fever, 6 gave a positive reaction. In 2 cases the infection occurred in the course of laboratory work. The series is of interest not only from the epidemiologic standpoint, but also because of the brief report of the clinical course of these 26 different cases. Incidentally, it is of some interest that none of the patients had come into contact with cows or hogs, but 14 of them used raw cows' milk. In 9 instances apparently there was contagious abortion infection of the herd from which the milk was obtained. Without the agglutination reaction there was no question that many of these severe infections would have been diagnosed severe cases of typhoid fever, influenza or even tuberculosis.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Fractures of the Upper End of the Femur.—SHAW (*Brit. J. Surg.*, 1928, **16**, 120) asserts that fractures of the narrow part of the neck are due to an axial twist of the femur, an indirect violence. Fractures of the broad part of the neck and intertrochanteric fractures are due to direct violence over the trochanter or to outward leverage of the shaft when head and trochanter are fixed. Fractures of the acetabulum are due to force transmitted directly along the capitocollar axis by violence applied immediately below the great trochanter. This axis runs through the center of the head of the femur and the great trochanter. Fractures of the pelvic girdle may be produced by the application of slowly increasing powerful pressure over the trochanters.

Hodgkin's Disease and Lymphosarcoma.—Coley (*Ann. Surg.*, 1928, **88**, 641) declares that lymphosarcoma and Hodgkin's disease should no longer be regarded as absolutely hopeless from any method of treatment. These tumors are, as a rule, extremely radiosensitive and are likewise responsive in a remarkable way to treatment with the mixed toxins of erysipelas and Bacillus prodigiosus. It would seem logical to use the combined treatment, thereby securing the advantage of the local effect of radiation (radium or Roentgen ray) and the system effect of the toxins which have the power to reach hidden and remote glands, beyond the reach of radiation. These patients should be kept under the closest observation for a long period of time and treatment should be kept up periodically for a number of years, especially in those cases in which the disease was generalized when treatment was begun. Cases of lymphsarcoma so treated should show a cure or at least a complete control for a long period (five years or more) in a very considerable number of cases, that is, 10 to 15 per cent. Typical cases of Hodgkin's disease still show a very bad prognosis and permanent control can be expected in only a very small number of cases.

Cancer in and About the Mouth.—Blair, Brown and Womach (*Ann. Surg.*, 1928, **88**, 705) state that cases are grouped into fairly definite anatomic sites chiefly because of their relation to treatment and prognosis and to facilitate classification, history taking and presentation. The term "carcinoma of the jaw" was not used, because bone involvement is secondary and only incidentally influences treatment. Growths with wide extension or metastases are put in the group corresponding to the primary growth site. Neck tumors do occur in which no primary growth site can be determined, but the majority of them are metastatic from some unrecognized upper respiratory or digestive-tract growth. In arriving at a plan of treatment and prognosis, clinical and microscopic findings are considered together. No one criterion has been found to offer a basis of prognosis accurate enough to present a percentage play to the patient of his chances of life. Biopsies are done in most cases before treatment is begun, both for confirmation of diagnosis and for studying the relative degree of malignancy of the growths. There has been observed a type of growth that in clinical aspects is cancer, but in which the microscopic picture does not show the typical definition of cancer. These growths may cause great destruction if not treated at least locally as cancer. The degree of malignancy of prostatic-gland carcinoma followed fairly closely that of the primary growth. There may be no microscopic evidence of malignancy in the regional glands, but this does not necessarily mean that the glands are not affected. Though results are, of course, best in the cases where no carcinoma was found in the glands, there are cases in the series that show that undifferentiated carcinoma even in the glands of the neck, is not an absolutely hopeless situation. There is a high operative mortality 21.5 per cent; all but one of the deaths occurring in advanced cases where very radical operations had been done. The farther back in the mouth and pharynx the operation is carried, the higher the mortality. This is probably due to increased liability to respiratory infection.

THERAPEUTICS

UNDER THE CHARGE OF

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Intracardiac Injection of g-Strophanthin.—FLECKSEDER (*Wien. klin. Wchnschr.*, 1928, **41**, 1253) reports strikingly favorable results in the restoration of the circulation from the intracardiac injection of doses of 0.5 to 0.75 mg. of g-strophanthin in cases showing extreme grades of circulatory failure due to collapse. The cases reported are those of severe intoxication by either morphin or lysol. Following the intracardiac injection of the warmed strophanthin solution the pulse which has been imperceptible rapidly returns and the heart beat becomes stronger, and within a few minutes to a few hours shows marked slowing. Initially, however, a period of rapid rate with irregular rhythm is often observed. In cases in which there is evidence of cardiac disease the method proved a failure. The author believes, therefore, that it should be limited to those instances of circulatory collapse which occur in patients with previously sound hearts, such as cases of severe intoxication and possibly those due to acute infection.

EDITOR'S NOTE.—The method as used by the author would certainly seem to be fraught with rather extreme danger to the patient, since in 1 or 2 cases the injection of strophanthin had been preceded by the intracardiac injection of fairly large doses of digitalis. However, since he is dealing with cases seemingly almost hopeless, such risks might be justified, although it is difficult to condone such a careless disregard of the synergistic actions of the digitalis bodies.

The Basis of Chemotherapy. SEIFFERT (*Klin. Wchnschr.*, 1928, **7**, 1497) presents a very comprehensive review of the accumulated facts with reference to the mechanisms involved in chemotherapy, and concludes that chemotherapeutic effects are dependent upon numerous and significant reactions in which the host participates actively. Direct parasitocidal action is only a part of the total actions. There seems to be little doubt that the phenomenon of drug fastness is dependent upon the chemical structure of the chemotherapeutic agent employed. Experimental and clinical observations show that there is very little if any valuable direct parasiticidal action involved, although the existence of marked specificity indicates the importance of some direct biologic action. The effort has been made to show that chemotherapeutic results are dependent exclusively upon a mobilization of the defenses on the part of the host, that is, as a special type of nonspecific therapy. The peculiar nature of these actions is ascribable to the special chemical structure of the agent employed, and the apparent specificity of its effects may be ascribed to its structure on the basis of its being organotropic.

The Actions of Insulin on Damaged Heart Muscle. Von Hagnal, Vidovszky and Gyorzi (*Klin. Wchnschr.*, 1928, **7**, 1543) follow up their own previous observations and those of other investigators which indicated the existence of possible detrimental action of insulin upon the heart in patients with diabetes. The present investigation is concerned with the effects of this agent in nondiabetic patients showing evidences of organic cardiac disease. Each of these patients was observed carefully for a preliminary period during which electrocardiograms were taken and each was then studied electrocardiographically after the administration of a fixed dose of 20 units of insulin. In 37 investigations made upon 33 patients, including 1 diabetic with angina pectoris, the following abnormalities are recorded: Sinus arrhythmia, twice; ectopic auricular beats, 6 times; atrioventricular rhythm with atrioventricular premature beats, 9 times; ventricular premature beats, 14 times; auricular fibrillation, twice; conduction disturbances, twice; bundle-branch block, once. When compared with similar observations on numerous noncardiopathic diabetic patients the incidence of electrocardiographic disturbance is seen to be much greater in the latter than in the former group. The disturbances of rhythm are not relieved by the injection of large doses of atropin or by the intravenous administration of glucose. Increase in cardiac rate is also shown to be independent of the hypoglycemia produced by insulin, and there is evidence to show that it might be due to an increased production of epinephrin. Changes in the form of the electrocardiogram are probably due to a direct action of insulin on the heart muscle, since they are not relieved by the administration of glucose. That these changes observed from insulin are often not harmless is evident from repeated clinical observations, especially where large doses of insulin have been required, as in cases of severe diabetes and where coma is present. The authors suggest that the administration of insulin to patients with myocardial damage should be coupled with the administration of large amounts of carbohydrate and that in cases with coma intravenous injections of sugar should be given simultaneously with insulin.

The Treatment of Rheumatic Diseases with Bee-sting Toxin.—Wasserbrenner (*Wien. klin. Wchnschr.*, 1928, **41**, 1255) presents a brief preliminary report on the use of a purified toxin from the sting of bees in 121 patients presenting such conditions as sciatica, neuralgia, chronic arthritis and arthritis deformans. He finds that this agent gives satisfactory results particularly in the group of patients with resistant forms of neuralgia, especially sciatica. The toxin is so purified as to be entirely free from protein, and it differs further from native bee-sting poison in not producing hemolysis. The most satisfactory method of administration, so far as favorable results are concerned, seems to be by intracutaneous injection. The initial dose is 0.2 cc., which is slowly raised to a maximum of 0.5 cc. Such injections produce only mild to moderate local reactions and are practically free from systemic reactions. After the first injection subsequent ones are administered only when the local reaction of the preceding dose has subsided.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Unclassified Types of Splenomegaly in Children.—Hitzrot (*Ann. Surg.*, 1928, **88**, 361) presents 3 cases of splenomegaly in children in whom the spleen was removed. In each case a shower of nucleated red cells appeared immediately after the splenectomy, and in 1 case this condition has existed for fourteen years, the nucleated red cells remaining in a proportion of 5 to 1 in the differential blood count up to the time of this report. In all the cases a few nucleated red cells were present prior to the operation, but the high percentage following splenectomy seemed a peculiarly constant feature not present in other cases of splenectomy studied by the author. Another feature present in all 4 cases was the onset of the disease in the second year with the appearance of a peculiar tint of the skin, bluish-white sclera, vomiting, loss of weight, loss of appetite and weakness. The third feature of interest was the lack of growth and development in these children. This arrested development also was markedly altered after the splenectomy. Two of the patients, after a short interval, began to grow normally, and to develop the mental traits characteristic of their real age. At no time did any of these children show any symptoms characteristic of rickets. Syphilis as a factor in all these cases can be eliminated. In 1 case malaria may have been a possible factor. No intestinal parasites were found in any of the cases. In the spleens there were no hyperplasias of the pulp cells, the Malpighian bodies seemed normal and the capsule and the trabeculæ were not thickened. There was no evidence of myeloidization and, except for a slight increase in the blood content, there were no significant symptoms. The structural changes in the spleen were slight and not characteristic of any definite clinical condition.

Clinical Results with Measles Streptococcus Toxin and Antitoxin.—Ferry, Gordon, Munro, Steele and Fisher (*J. Am. Med. Assn.*, 1928, **91**, 1277) present a joint report of the work done in several institutions. At the Children's Hospital, where the treated patients were controlled with an equal number of untreated patients under the same conditions, the computed actual protection following the use of 20 cc. measles streptococcus antitoxin was 88 per cent. At the Herman Kiefer Hospital, where the patients treated with 10 cc. of measles streptococcus antitoxin were well controlled with a much larger number of untreated cases, as well as a larger number of patients treated with 5 cc. of measles convalescent serum, the actual protection afforded by the measles streptococcus antitoxin was 42 per cent, as compared with 19 per cent of those cases treated with measles convalescent serum. At the Children's Convalescent Home, where the susceptible individuals

were picked according to their reaction toward measles toxin, the positive skin reactors being considered susceptible, the computed actual protection, when the cases were controlled with an equal number of untreated cases, was 67 per cent. The average computed actual protection shown in the three series of cases in the three institutions was 66 per cent, and at the two institutions where the dose was 20 cc. the average protection was 78 per cent. This was apparently far superior to the computed actual protection afforded by the measles convalescent serum which was determined in the same series under the same conditions and controlled with the same untreated patients. In the Children's Convalescent Home it was shown in 13 out of 13 cases that infection and recovery from measles changes a positive reactor to a negative reactor. This, with the fact that diluted measles convalescent serum will neutralize measles toxin, speaks in favor of the proof of the specific relationship of measles toxin from Streptococcus morbilli to measles, and argues in favor of the use of measles streptococcus antitoxin, prepared from this toxin as a protective measure against the disease.

Observations of So-called Influenza Infection in Children.—McLean (*Arch. Pediat.*, 1928, **45**, 571) states that influenza is as much a seasonal disease as are measles and whooping cough. There is a direct proportion between the decrease in influenza and the increase in measles. The same is true of measles and pertussis. The complications of influenza are the same as those of measles. The complications depend on management, physical condition of the patient, age and climatic conditions. Younger children are more apt to have recurrences and relapses than older children. One attack during a season predisposes to relapses, recurrences and reinfections. Either age or repeated attacks from year to year seem to confer a certain amount of immunity. The disease, when transmitted from one individual to another has a tendency to produce the same type of infection. In 361 patients of all ages definite recurrence appeared in 119 or 32.8 per cent. The average number of days of recurrences in patients of all ages was forty-five years. During October and November asthmatic bronchitis is the predominating type of infection. In February and March the gastrointestinal type predominates.

Blood in the Stools of the Newborn.—Bonar (*Am. J. Dis. Child.*, 1928, **36**, 725) found the benzidin test for occult blood positive in 29.38 per cent of 1518 stools of 109 newborn babies. Occult blood is found too frequently in the stools of the newborn to ascribe its cause to the usual sources. It should not be considered physiologic. Certain observations seem to warrant the assumption that the bleeding is due to an intense hyperemia set up in the upper portion of the small intestine by the first products of digestion, by the primary bacterial invasion or by both. More attention should be given to the initial diarrheas of the newborn, which appear to be another manifestation of the irritability of the bowel which occurs in the early days of life.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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AND

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Comparative Hysterectomy Results.—As the general surgeons squabble over the relative advantages of cholecystectomy and cholecystostomy, so the gynecologists are still trying to standardize hysterectomy. The difficulty encountered in comparing different series of hysterectomies from different clinics is that not only are they done by different operators, but they are done for widely variant lesions and, therefore, comparisons are obviously unfair. In order to make a careful and fair comparison of the supravaginal, complete and vaginal hysterectomy, a study was made by BAUER (*Am. J. Gynec. and Obst.*, 1928, **15**, 680) in the Presbyterian Hospital, Chicago, taking an equal number of each type of operation, performed upon patients with the same type of lesion and who were in apparently the same physical condition before operation. From his study he found that it is safer to remove the uterus by vaginal hysterectomy when it is possible to do so. No deaths occurred in this group and there is a definite decrease in the morbidity. Twice as many cases were afebrile in this group as compared to the other two types of hysterectomy. In regard to the abdominal types of hysterectomy he found an increase of 50 per cent in the morbidity when the cervix is removed and the average convalescence is increased by nearly four days. On the other hand, only one case in the group of supravaginal hysterectomies returned for removal of the cervix and that was for a benign polyp. He concludes that the routine removal of the cervix for fear that malignancy or other disease might develop does not seem to be warranted when one considers the increased morbidity incident to its removal; to which conclusion we heartily subscribe. We do not agree, however, that the vaginal approach is preferable to the abdominal as a general rule but only in the hands of those who have been trained in clinics where this form of approach has always been popular. In average hands we believe that abdominal supravaginal hysterectomy will give the best postoperative results and lowest morbidity. It is by far the commonest type of hysterectomy performed in our clinic.

Chancre of the Cervix.—In discussing this subject and in presenting their experiences with such cases, STOOKEY and ROBERTS (*Am. J. Syph.*, 1928, **12** 212) state that the cases of primary syphilis occurring upon the cervix in their series have been diagnosed entirely in women who had early secondary syphilis without external evidence of a chancre. In short, the cervix has been carefully investigated in every case of early

secondary syphilis. In contrast to their conception of the classical picture of the initial lesion of syphilis, the results have been startling. The most striking finding has been the lack of definite areas of indurated ulceration and the presence of edema. This edema, they believe, is the most constant outstanding clinical observation in the diagnosis of a primary syphilitic infection in women. Histologically, cold edema presents all the characteristics of early syphilitic infection aside from the fact that there is no necrosis of tissue, or in other words, round-cell infiltration of the blood and the lymph spaces is productive of edema without definite ulceration. The edema characteristic of syphilitic infection pits on pressure, is cold to the gloved examining finger and shows no tendency toward suppuration or fluctuation. As a result of their observations they are convinced that the primary lesion of syphilis is extremely common upon the cervix and without clinical diagnostic characteristics. The subjective sensations produced by a chancre on the cervix are almost negligible. Pain is absent, discharge is scanty and hemorrhage is usually absent. If this contention of Stookey and Roberts is correct we will all have to change our conceptions of the clinical appearances of primary syphilis of the cervix. Their paper is well written and should be seriously considered because although syphilis is usually transmitted to the female by the vagina, those of us who have had many years of gynecological experience must confess that the typical chancre is rarely seen on the cervix.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Ethmoiditis in Infants and in Young Children with Accompanying Eye and Orbital Complications.—THEISEN (*Arch. Otolaryngol.*, 1928, **8**, 386) in a study of 31 cases of ethmoiditis, found in the six youngest patients with sinusitis, eye or orbital complication. Their ages ranged from two to twenty months. The diagnosis of sinusitis in all cases was based largely on roentgenograms. Orbital complications, particularly orbital abscess, made radical operation on the ethmoid bone imperative. In such cases an external operation was performed. One child, aged six months, had acute ethmoiditis with orbital abscess and exophthalmos. An infant, aged ten months developed orbital abscess about ten days following the onset of nasal discharge which came from the ethmoids. A child, aged ten months, developed ethmoiditis followed by great swelling of the lids and inflammation of the eye, orbital abscess, exophthalmos, with infiltration and swelling in the inner canthus. An infant, aged twelve months, developed ethmoiditis, the lids became edematous and inflamed, chemosis of bulbar conjunctiva, no exophthalmos, localized infiltration and swelling of the inner angle of the eye. An infant,

aged ten months, developed ethmoiditis, ten days later orbital abscess and exophthalmos developed. In the cases of ethmoiditis in young children with external rupture, the rupture usually occurs at the inner angle of the eye, with the appearance of an infiltration and swelling. In young infants, spontaneous rupture may follow closely an acute ethmoiditis.

Infection of the Eye; Report of a Case of Anthrax of the Eyeball.—CLARK (*Int. J. Med. and Surg.*, 1928, **41**, 436) treated a boy whose cornea was penetrated by a flying piece of rock. Shortly following this the boy became acutely ill with malaise, dry and parched skin, temperature 99.5°, pulse 98. The eye was inflamed and presented a yellow appearance with a greenish tinge extending over the iris and posterior cornea. All tissues of the eye rapidly became swollen and a small area of gangrene developed. The eye was enucleated with practically no bleeding. Bacteriological examination revealed anthrax bacilli. The organism was acquired from a baseball mitt, the wool padding of which was cultured and the anthrax organism found.

Corneal and Scleral Anesthesia of the Lower Half of the Eye in a Case of Trauma of the Superior Maxillary Nerve.—VONDERAHE (*Arch. Neurol. and Psychiat.*, 1928, **20**, 836), observed a patient who suffered a comminuted fracture of the left malar bone. Six weeks after the injury examination revealed paralysis of the left abducens, anesthesia of the lower half of the left eye and the left side of the face, and weakness of the left masseter muscle. The cornea and sclera are reached by the short and long ciliary nerves from the ophthalmic division of the trigeminal, but the author believes from observation of this case that a great portion, if not all, of the sensory fibers to the lower half of the cornea and sclera are supplied through the superior maxillary division of the fifth nerve.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Irrigations with Aqueous Solutions. Their Effect on the Membranes of the Upper Respiratory Tract of the Rabbit.—Irrigation of the nasal fossæ with aqueous solution has been advocated for many years in the treatment of various lesions of the nose. As a rule, the potential disadvantages and untoward sequelæ of this almost universally practised procedure have not been recognized, although attention to them has been directed in a previous review in these columns ("A Harmless Mucous Membrane Irrigant"—FISCHER and BLEDSOE AM. J. MED. SCI., November, 1927). As a first step in ascertaining the histologic changes of the nasal mucosa occasioned by irrigation, STARK (*Arch.*

Otolaryngol., 1928, **8**, 47) conducted a series of experiments on 24 normal rabbits, using 8 others for controls. The rabbit was selected as the experimental animal because its nose is very similar to that of man, anatomically, histologically and physiologically. The irrigating fluids consisted of 0.9 or 2 per cent sodium chloride solution, or tap water—all at a temperature of 40° C. At necropsy, 75 per cent of the rabbits irrigated were found to have mucopurulent secretion in the nasal fossæ and in the paranasal sinuses. Almost half (45 per cent) of which showed a bilateral involvement of the sinuses. The reaction of the nasal mucous membrane was less marked to the isotonic solution than to the hypotonic or hypertonic. The macro- and microscopic mucosal changes consisted of hyperemia with leukocytic infiltration, increased glandular activity, and increased in the size of vacuoles and epithelial cells.

New Histopathologic Findings in the Ear in Lues and their Importance in the General Pathology of the Ear.—In the early studies of the histopathology of the ear, it was believed that the many characteristic findings for the various congenital and acquired aural diseases were known. With the increase of our knowledge, however, less certainty as to the specificity of these lesions was entertained. After mentioning the prominent histopathologic findings in otosclerosis, Paget's disease, cretinism and the "choked labyrinth," ALEXANDER (*Laryngoscope*, 1928, **38**, 295) presented the histologic changes which occurred in the ears of 6 patients with acquired syphilis—all of whom had been examined clinically during their lifetimes. Some of the outstanding lesions consisted of gumma in the cochlear capsule, ankylosis of the stapes, obliteration of the cochlear window and aqueduct (all of which have been described in otosclerosis); marked ectasia of the inferior parts of the inner ear, as is seen in Paget's disease; the occurrence of fat in the internal ear similar to the picture observed in cretinism; different degrees of atrophy in Corti's organ and in the nerve ganglion apparatus, simulating the findings caused by arteriosclerosis; and complete or incomplete closure of the cochlear aqueduct as is found in a "choked labyrinth" caused by brain tumor. The author dwells on the possibility that otosclerosis may be caused by syphilis and suggests that antiluetic treatment be instituted as an active and prophylactic therapeutic agent. He concludes by emphasizing that great diminution in hearing can be caused by changes in the conductive apparatus alone, with no changes in Corti's organ or in the nerve ganglion apparatus—as was found in one of the reported cases.

Studies of Pathologic Tissue Removed from Chronically Infected Nasal and Accessory Sinuses.—In a preliminary report of the histologic changes encountered in a selected group of patients suffering from disease of the nasal and accessory nasal sinuses, MULLIN and BALL (*Ann. Otol., Rhinol. and Laryngol.*, 1928, **37**, 128) tabulated the findings of 32 cases. For convenience, exclusive of neoplasms, the histologic changes were classified into four groups—edema, fibrosis, leukocytic reaction, and glandular hyperplasia or atrophy. No constant finding was present which would enable one to correlate a definite group of

symptoms with the pathologic lesions. In the asthmatic cases the histopathologic lesions and the symptoms were the most closely related, but even among these the findings were not constant. The most severe type of sinus infection, as judged by destruction of tissue and the polymorphonuclear leukocytic reaction, was found in cases of bronchitis and of cough without local pain. Certain changes were sufficiently constant, however, for their absence to permit a negation of the presence of a disease process in the sinuses.

A Further Discussion of Affections of the Optic Nerve Due to Sinus Disease.—In discussing the same subject COFFIN (*Ann. Otol., Rhinol and Laryngol.*, 1928, **37**, 165) differs with Loeb's conclusion that the bacteria or toxins from the diseased sinus are borne either arterially or lymphatically direct to the nerve, claiming that the affection of the optic nerve is brought about mechanically by the disturbed circulation of the parts and that the changes in the nerve might as easily be produced by infection of a sinus most distant from the nerve. Coffin emphasizes another not generally recognized manner of disturbance of the optic nerve from sinusitis, namely, a phlebitis of the ethmoidal and ophthalmic veins. Clinical comparisons are made, and pictures are reproduced, to substantiate his ideas.

Ligation of the External Carotid Artery for Persistent Nasal Hemorrhage.—In cases of severe spontaneous, traumatic or postoperative arterial hemorrhage about the nose or throat, in which ordinary hemostatic measures fail, carotid artery ligation furnishes a formidable controlling procedure. As most of these regions are supplied by branches from the external carotid artery, ligation should be limited to it—particularly in view of the fact that less danger ensues than in ligation of the common carotid artery. After a consideration of the surgical technique involved, ABRAHAMS (*Arch. Otolaryngol.*, 1928, **8**, 29) reports a case of serious recurrent nasal hemorrhage following an operation on the right ethmoidal and sphenoidal sinuses, wherein ligation of the right external carotid artery proved effective.

RETROSPECTOR'S NOTE.—The retrospector takes this occasion to mention a case of severe, persistent epistaxis from the left antrum following extensive fracture of the malar bone; in which recovery followed left external carotid artery ligation after all other attempts to control the bleeding had failed.

Radical Operation on the Mastoid. End Results in 100 Unselected Cases.—Stating that a radical mastoidectomy is successful when it prevents intracranial infection, stops or lessens aural discharge and offensive odor, relieves headaches and vertigo, and preserves the hearing, WHITE (*Arch. Otolaryngol.*, 1928, **8**, 32) has found, in the analysis of the end results of 100 unselected cases, that the procedure is largely successful. Fifty-seven of the radical operations were completely successful and the remainder resulted in a decided decrease of discharge and odor. Only 3 had intracranial complications. The hearing was improved in 37, unchanged in 14 and lost in 49. It is interesting to note that the poorest results occurred in all cases in which the discharge

had existed for less than a year; and that the most favorable results were seen in those cases with a discharge of from five to fifteen years' duration. Tonsillectomy was beneficial. Headaches and vertigo were relieved in 84 and 70 per cent, respectively, of those individuals so afflicted.

The Histology and Pathology of the Articulation of the Auditory Ossicles.—In studying many microscopic sections of normal and pathologic aural states in Alexander's laboratory, Druss (*Arch. Oto-laryngol.*, 1928, **8**, 56) observed that the normal articulations of the malleus and incus and stapes consist of four layers in each ossicle: bony, calcified cartilage, hyaline cartilage and a variable terminal layer resembling fibrocartilage, connective tissue, endothelium, and so forth. In his opinion, the articulation is not that of a real jojnt, but rather a type of symphysis between the two ossicles. Ankylosis of the ossicles was of comparatively frequent occurrence and may be classified in the group of normal and considered a phylogenetic variety. The articulations were seldom the site of pathologic lesions, due in all probability to the resistant capsule surrounding the joint. In only 1 case of the 37 examined, including 16 cases of suppuration of the middle and inner ear, was there also suppuration within the joint.

RADIOLOGY

UNDER THE CHARGE OF

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Roentgenologic Manifestations in Eighty-seven Cases of Gastric Syphilis.—In the records of the Mayo Clinic from 1913 to the present Moore and Aurelius (*Am. J. Roent. and Rad. Ther.*, 1928, **19**, 425) have found 87 cases in which the evidence of gastric syphilis was convincing. Of the patients 60 were men, 27 were women. Predominance of the disease in the fourth and fifth decades of life was indicated by the fact that 41 of the patients were between thirty and forty years of age and 26 were between forty and fifty years; the youngest patient was twenty years, and the oldest sixty years of age. In most patients of the series there was marked loss of weight, epigastric pain or distress, vomiting, achlorhydria, anemia without cachexia, and rarely hematemesis (4 of the 87), these symptoms constituting the syndrome so frequently described. Based on the roentgenologic manifestations three major types were distinguishable: (1) prepyloric; (2) median or hour-glass; (3) diffuse. Seventy per cent of the cases were of the first or prepyloric type, in which the deformity adjoined the pylorus and

extended proximally in varying degrees. Almost without exception the defect was concentric and rather symmetric. As a rule, contraction was pronounced and the lumen narrowed progressively toward the pylorus, resulting in a spicular form of the barium shadow, although in many instances it was of tubular shape with constant diameters. Whether short or long, the contracted lumen pursued a straight or fairly direct course and was never markedly tortuous; occasionally its margins were quite smooth but more often they were slightly irregular. Second in frequency was the median type comprising 22 per cent of the series. In this type the pyloric and cardiac extremities of the stomach were not involved and the lesion was confined to the segment between them producing hour-glass deformity. As in the first type, the filling defect tended to be concentric and symmetric, and the lumen of the constricted area was relatively smooth. A notable feature in most of these cases was the great length of the constriction so that the shadow of the deformed stomach resembled a dumbbell rather than an hour glass. Only 8 per cent of the cases were of the third type, with such diffuse involvement that little of the stomach remained normal. Here again concentric contraction was dominant. Though obvious in all cases, it varied in degree and in one instance was so extreme that the distal three-fourths of the gastric lumen was represented by a scarcely visible thread of barium while the cardiac segment was reduced to a small pouch. All three types had features in common. Peristalsis was lacking in the deformed area and was seldom active in the unaffected portion. Gaping of the pylorus was observed frequently. Even with marked narrowing, gastric residues and dilatation above the stenosis were rare. Most important of all was the rarity of a palpable mass. Often there was a vague sense of resistance but only once was a tumor felt distinctly, Despite numerous simulants, such as cancer, hypertrophy of the pyloric ring and gastrospasm from extrinsic causes, the authors feel that the Roentgen diagnosis of syphilis is possible in a high percentage of cases. This disease is always to be thought of in cases with a long, central hour-glass, or prepyloric narrowing without a palpable tumor, or when a patient has a lesion resembling scirrhous cancer but is relatively young, or when the patient is neither cachectic nor greatly weakened notwithstanding extensive disease of the stomach.

Some Pseudovesicular Shadows and Other Pitfalls in Gall Bladder Roentgenology.—In the direct examination of the gall bladder without the aid of cholecystography, CASE (*Radiology*, 1928, **11**, 1) is of the opinion that a small rounded ovoid shadow in the right upper quadrant, distinctly not caused by the inferior border of the liver or kidney, is in all probability due to something else than the gall bladder. This is shown by the fact that the shadow may appear in patients from whom the gall bladder has been removed and by the further proof that the gall bladder visualized by the Graham method does not coincide with the ovoid shadow mentioned. Case believes that this shadow is usually made by the first portion of the duodenum, or by one of the small lobes of the liver, or by the pyloric end of the stomach. The same explanations apply to the rounded, so-called "gall bladder impression" of the first part of the duodenum, formerly attributed to pressure of the gall bladder.

On the Relationship of the Ingestion of Fats to Emptying of the Gall Bladder.—SILVERMAN and DENIS (*Radiology*, 1928, **11**, 45) were able to confirm Boyden's findings that the ingestion of cream and egg yolk together or separately produces appreciable emptying of the gall bladder. Nonemulsified fat (olive oil) had practically no effect on the shadow of the gall bladder. In none of the patients examined was there a great increase of fat in the blood at the time the gall bladder was emptying.

The Normal Cholecystographic Response.—In a series of 251 patients responding normally to cholecystography at the Mayo Clinic, and later operated on for various abdominal lesions, 19 per cent were found to have disease of the gall bladder. KIRKLIN (*Radiology*, 1928, **11**, 34), therefore, points out that positive cholecystographic diagnoses have a higher percentage of accuracy than negative diagnoses. In 37 cases, or nearly 15 per cent of the series, definite cholecystitis without stones was found at operation, although the cholecystograms were normal in every respect; Kirklin thinks that the percentage of normal responses in such cases is probably higher than is generally believed. In only 10 instances were stones found, and these were mostly small and few in number. In conclusion, the author points out that while the gall bladder is believed to be sensitive to autonomic nervous influences, its behavior in the cholecystogram as observed in this series is apparently seldom affected by duodenal ulcer, chronic appendicitis, pelvic lesions and many other diseases of abdominal organs.

Cholecystography in the Late Months of Pregnancy.—Among seventeen primiparæ examined by LEVYN, BECK and AARON (*Radiology*, 1928, **11**, 48) the intravenous injection of sodium tetraiodophenolphthalein produced no harmful effect on the mother, fetus, or the course of the pregnancy. In 10 the concentration of the dye and response to the Boyden meal were normal; in all these cases the gall bladder occupied a high position, and in 6 instances pressure defects in the shadow were demonstrable. The authors do not believe that the failure to obtain a shadow in 7 cases was due to pressure but leave the implication that it was due to disease of the biliary tract which was probably of metabolic origin. Morning sickness occurred more often in the patients in which no shadow of the gall bladder was obtained. It is suggested that during the entire course of pregnancy a properly balanced fatty meal be taken daily to stimulate emptying of the gall bladder and prevent stagnation of the bile with the precipitation of cholesterol and the formation of stones.

In the general discussion of the foregoing paper Sherwood Moore, who has been intimately associated with Graham in the development of cholecystography, said that the intravenous administration of the dye is perfectly safe both in pregnancy and during the puerperium. He had given the drug in this manner to 28 patients in the late months of pregnancy. On the other hand, Conyers, in further discussion, stated that he did not give the drug in cases of pregnancy, as several women had menstruated freely fifteen to twenty minutes after taking the dye, and a number of women had severe uterine cramps following the injection.

Roentgenologic Aid in the Diagnosis of Ileus.—Case (*Am. J. Roent. and Rad. Ther.*, 1928, **19**, 413) again shows that the widely dilated gas distended loops of bowel characteristic of ileus, are demonstrable with the Roentgen ray, and usually without the aid of a barium meal or enema. Roentgen ray study can be made at the bedside, disturbing the patient little if at all. In general, obstruction of the small intestine is indicated by irregular gas areas, mostly in the center of the abdomen, and gas collections over fluid levels, more broad than high. Usually the diaphragm is not elevated. Often the wall of the bowel is not seen, but when visible exhibits Kerkring's folds as a herring-bone effect. Sometimes the gas distended segments lie parallel to each other like the steps of a ladder. The method is of special value immediately after operation in abdominal cases, and, in the absence of dilated intestinal loops, the presence of ileus is to be doubted.

Tissue Changes after Salvarsan and Bismuth Injections.—Leeser (*Fortschritte a. d. Geb. d. Roent.*, 1928, **37**, 486) describes 3 cases in which dense shadows were demonstrable in the pelvis after intramuscular injections of salvarsan or bismuth. The patients were children two or three years of age who had been treated for congenital syphilis. In 2 instances the injected drugs had evidently been completely absorbed and the shadows which remained were attributed to myositis ossificans set up by irritation. Whatever the cause of the shadows, they might easily be misinterpreted by the roentgenologist if he is unaware of the patient's history.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Tuberculoma of the Central Nervous System.—Anderson (*Arch. Neurol. and Psychiat.*, 1928, **20**, 354) analyses 27 cases and reports: Average age in 22, 31.8 years; males, 77.7 per cent; solitary tubercles, 74 per cent; size of tumors ranging from 2 by 2 cm. to 4 by 8 cm.; location showed no predilection for either side but the majority of the lesions were supratentorial; the weight of the brain was not increased but the volume appeared generally larger than normal; meningitis was present in 77.7 per cent; tubercle bacilli were noted in the spinal fluid only once in the series; spinal fluid cell counts ranged from 2 to 320; as to incidence among tumors, tuberculomas constitute 15 per cent. He considers that the tumor syndrome may be present but is usually eclipsed by the signs of meningitis.

Lesions in the Brain and Death Caused by Freezing.—BENDER (*Arch. Neurol. and Psychiat.*, 1928, **20**, 319) finds that in 1 human being, 1 guinea pig and 1 rabbit that were frozen to death, congestion and miliary hemorrhages in all parts of the brain. There was also marked pulmonary congestion. In the human brain the nerve cells also showed severe vacuolization. She considers these changes to be due to the forcing of the blood to the brain by the peripheral ischemia. The fact that the vacuoles did not occur in the nerve cells of the lower animals she considers due to their smaller size, their lower grade of specialization or to the shorter period of exposure to the cold. She takes issue with the common statements in the literature that the anatomic changes due to death by freezing are not distinctive.

Tumors of the Nervus Acusticus, Signs of Involvement of the Fifth Cranial Nerve.—PARKER (*Arch. Neurol. and Psychiat.*, 1928, **20**, 309) finds signs of involvement of the fifth nerve in all but 1 of 53 proved cases of tumor of the acoustic nerve and these signs were second in importance to those of injury to the eighth nerve. Parasthesia was common and in 5 cases it antedated the symptoms of involvement of the eighth nerve. Anesthesia and weakness of the muscles of mastication were less marked. Disturbance of the corneal reflex was present in 5 cases. Pain occurred in 4 cases in 1 of which it was identical with that of tic douloureux. Because of the frequency of involvement of the fifth nerve and its early occurrence, the author considers a careful examination essential where symptoms suggesting a tumor of the acoustic nerve are present.

Studies in Epilepsy, the Fibrin Content of the Blood.—LENNOX (*Arch. Neurol. and Psychiat.*, 1928, **20**, 345) reports the measurement of blood and plasma fibrin in 100 patients with epilepsy and finds the average concentration of fibrin in the plasma approximately 19 per cent above the average concentration for normal persons obtained by Foster. The concentration of plasma fibrin was abnormally high in 34 of the patients. In only 7 of these could the increase be accounted for by pyogenic or syphilitic infection and in the remaining 27 patients the cause of the increase was not apparent. He advises further investigation with simultaneous measurement of the speed of coagulation of the blood, of the sedimentation of the red cells and of the concentration of the other plasma proteins.

Acute Toxic Encephalitis in Childhood.—GRINKER and STONE (*Arch. Neurol. and Psychiat.*, 1928, **20**, 244) present a clinicopathologic study of 13 cases. They review the literature on the subject. Five of their cases occurred with severe neurologic symptoms and a definite focus of infection; 2 with severe neurologic symptoms and a fulminating septicemia; 1 with severe neurologic symptoms of undetermined origin; 2 without severe neurologic symptoms with focal infection; 1 occurred with scarlet fever. All the above came to necropsy. Two additional cases with neurologic symptoms and of focus of infection recovered. The postmortem observations formed a fairly uniform group. Macroscopically, the brain showed hyperemia with engorged leptomeninges,

the subarachnoid space slightly distended with fluid, and the cut surfaces reddened and studded with visibly dilated vessels. The authors do not consider the macroscopic appearance of hyperemia as pathognomonic of encephalitis. The important findings microscopically were the absence of mesodermal infiltration, a profound destruction of ganglion cells, and changes in the local vascular system consisting of new vessel formation and stimulation of the vascular endothelium often leading to obliteration of capillaries. There was also a marked proliferation of the glia cells quite constantly found consisting mainly of cystoplasmic glia and oligodendroglia with few Hortega cells and no free mobile glia cells. The microörganism recovered from the focal infections or from the blood was a staphylococcus or a streptococcus. The focus of infection constituted in most instances the initial complaint. Spinal fluid examinations were entirely negative excepting in one case. The infections encountered were usually those of the upper respiratory tract, infections of the ear and mastoid, pneumonia, scarlet fever and septicemia. The clinical course they found fairly uniform: "rapidly developing symptoms of diffuse cerebral involvement, often associated with meningeal symptoms; early stupor; hyperpyrexia and death in from three to four days." They believe the toxic agent exerted its influence by a hematogenous route. The suggestion is made that severe neurologic sequelæ may develop from acute toxic encephalitis associated with acute infections if recovery occurs and that more attention should be directed to encephalitis as an etiologic factor in these sequelæ.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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"Filtrable Forms" of the Tubercle Bacillus.—In recent years a very great interest has been aroused in the question of filter-passing forms of the tubercle bacillus, and the European, particularly the French, literature is filled with papers on this subject. COOPER and PETROFF (*J. Infect. Dis.*, 1928, **43**, 200) in a critical review of the rather confusing reports have indicated certain possible or probable errors in technique and have added a number of observations of their own. Two angles of the problem are particularly discussed. The first is the filtration of various tuberculous materials through Chamberland and other filters and the inoculation into animals of, and attempts to obtain growth from the filtrates. Very rarely indeed was either a positive culture or a positive tuberculous process obtained in the guinea pigs and these that did occur may have been the result of a chance passage of the filter by the whole tubercle bacillus. However, the mass of evidence supporting

the occurrence of the filtrable forms has been the finding of acid-fast rods in the swollen, but not caseous, lymph nodes and the development of cachexia in the inoculated animals. The first observations are greatly weakened in their significance by the finding of acid-fast organisms in the lymph nodes in 33 per cent of normal or at least uninoculated guinea pigs by the authors and the development of cachexia is known to follow inoculation of foreign proteins, and may be the result of intercurrent disease and infections such as in the middle ear or the sinuses. The second angle of the problem is concerned with the possible passage of the filtrable form from mother to offspring. The general evidence is that tubercle bacilli are transmitted very rarely from mother to offspring when the placenta is perfectly normal and free from tuberculosis. Moreover, placental tuberculosis is not nearly as rare as is generally supposed and that in clinically active tuberculosis it is very probable that the permeability of the bloodvessel wall may be so altered as to permit, without actual placental infection, the escape into the fetal blood of intact whole organisms. These suggestions indicate that congenital tuberculosis when it does occur can be explained without the involvement of filtrable forms of the bacteria. There is little known about the life cycle of the tubercle bacillus and the occurrence of filtrable forms should not be ruled out if the evidence is satisfactory, but at present it is not necessary to accept the hypothesis of filtrable forms to explain the facts at hand.

The Dick Test and Allergy.—The skin reaction to the toxin of the scarlet fever streptococcus is so irregular following antigen administration that HARDY (*Proc. Soc. Exper. Biol. and Med.*, 1928, **25**, 725) believes the explanation is to be found not in toxin reaction and antitoxin production but rather in considering the phenomena as examples of allergy. A negative Dick test may signify that an individual has not yet been sensitized, or has been sufficiently stimulated to have developed circulating antibodies, which mask the allergy.

Regional Vaccination.—General vaccination by subcutaneous injection has been rather disappointing as a curative measure in many infections. Local vaccination as advocated by Besredka has been receiving recently an increased attention and now POINCLOUX (*Comp. rend. Soc. de biol.*, 1928, **99**, 287) advocates a third method of immunization—vaccination at the portal of entry or regional vaccination, using the word regional to include the tissues at the portal of entry of the pathogenic germ and the organ in which the germ has become established and is doing damage. He reports, in gonococcus and other infections of the cervix uteri, that with minimal amounts of auto vaccines (5 drops) he obtained a violent reaction and favorable results only when he injected his vaccine at the actual portal of entry. Further reports on the application of this principle of treatment (Poincloux and Weissmann, *idem*, p. 290) gives the results in patients with salpingitis, three infections by the gonococcus and one by the colon bacillus; in many patients with metritis (*idem*, p. 374) and in two with chronic gonorrheal urethritis and one with acute gonorrheal rheumatism (*idem*, p. 469). The benefit from this method of treatment was very encouraging.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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An Epidemiological and Statistical Study of Tonsillitis, Including Related Throat Conditions.—COLLINS and SYDENSTRICKER (*Pub. Health Bull., No.* 175, July, 1927) present an exhaustive statistical study. The more important points in the summary are as follows: "Tonsillitis and other throat conditions appear to constitute 5 to 10 per cent of the measurable illness from all causes and from 15 to 20 per cent of the illness due to respiratory diseases. Cases of tonsillitis and sore throat seem to be much more frequently accompanied by general symptoms such as fever, aching, chilliness, and constipation than cases of coryza or bronchitis. The incidence of tonsillitis and related conditions of the pharynx is higher among children of school ages than before or after those ages. Laryngitis, on the other hand, appears to occur more frequently among adults than among preschool or school children. tonsillitis and related conditions of the pharynx appear to be the only important respiratory affection which shows this particular age incidence, that is, higher during the school ages than among younger or older persons. The incidence of tonsillitis and related conditions of the pharynx appears to be considerably higher for females than for males. Unlike other respiratory conditions, the reported incidence of tonsillitis and related throat conditions apparently does not increase during periods when influenza is epidemic. Nor is there evidence of important independent epidemics of tonsillitis and other throat conditions, except septic sorethroat. There is, however, a fairly regular seasonal variation in the incidence of these diseases. Tonsillitis and related throat conditions are relatively unimportant as causes of death. In about 75 per cent of the deaths in which some disease of the pharynx is involved, some other cause is specified either as the primary or a complicating cause of death. The most common diseases certified as joint causes with diseases of the pharynx are, in the order of their frequency, heart disease, pneumonia, septicemia, nephritis, rheumatism, bronchitis and tuberculosis. The frequency of tonsillectomy varies greatly in different sections of the country. In general, the more urban the district the more tonsillectomies are performed. Tonsillectomy rates in the Army and Navy are five to ten times as frequent now as they were about 1910. Tonsillectomy does not account for all the decrease in the prevalence of defective tonsils with increasing age. The incidence of certain nonrespiratory diseases varies with the condition of the tonsils.

The incidence of illness from rheumatism, heart conditions, cervical adenitis and ear conditions tends to be lowest among children with normal tonsils, higher among those with defective tonsils, and highest of all among those with removed tonsils. Presumably these more or less chronic conditions clear up only slowly, if ever, after the tonsils have been removed. For this type of condition, special treatment in addition to the removal of the tonsils may be necessary. The incidence of illness from rheumatism and related conditions appears to be higher among adults who have attacks of tonsillitis than among those who are free from tonsillitis. The incidence of diphtheria among children with defective tonsils seems to be much higher than among children with removed tonsils. Among children with normal tonsils it appears to be only slightly higher than among those whose tonsils have been removed. The incidence of measles, whooping cough, chickenpox, and mumps all appear to be higher among children whose tonsils have been removed than among either of the groups with the tonsils present. Similar differences are indicated by rates based on susceptible children only, eliminating from consideration all children who had suffered a recognized attack of the disease prior to the period of observation. A higher proportion of children with removed or normal tonsils were judged on clinical evidence to be of excellent or good nutrition than in the case of children with defective tonsils. However, the hemoglobin index in a small group of children did not reveal any difference among the various tonsil groups with respect to nutrition as indicated by this index. Height and weight measurements and records of growth in weight over a period of nine months for a group of school children did not show any advantage in the growth of one tonsil group over another."

PHYSIOLOGY

PROCEEDINGS OF

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The Nature of the Hyperglycemia Associated with Anaphylactic Shock in the Dog.—ISOLDE T. ZECKWER and J. ERNEST NADLER (from the Department of Pathology, University of Pennsylvania). It has recently been shown that hyperglycemia accompanies anaphylactic shock. The present study is an attempt to determine the mechanism of this phenomenon, and to gain further data on the factors which are involved in the release of glycogen from the liver. The experiments were carried out on dogs because of the apparent absence of the asphyxial factor in anaphylaxis in this animal. The dogs were divided into two groups: (1) intact animals, and (2) dogs in which the left adrenal had been excised and the right splanchnic nerve cut long previous to the acute experiment. Both groups of animals were sensitized to horse serum.

At the time of the acute experiment, the dogs were given amytal as an anesthetic which has little effect on the blood-sugar level; artificial respiration was instituted to offset any respiratory disturbance; blood pressure was recorded; and frequent blood-sugar determinations were made preliminary to the induction of anaphylactic shock by the injection of serum, and at frequent intervals after onset of shock.

Nine unoperated dogs showed a rise in blood sugar during shock, the mean increase above the preliminary level being 0.057 ± 0.006 gm. Six dogs which had been operated upon showed a relatively lower hyperglycemia, the mean increase being 0.026 ± 0.004 gm. In the latter, determinations of liver glycogen at the end of the experiment proved the presence of available glycogen.

Determinations of the oxygen content and percentage unsaturation of the arterial blood before and during shock ruled out the possibility that the hyperglycemia was due to inadequate ventilation.

The rise in blood sugar, which occurs in spite of the loss of adrenal activity, is considered probably due to the venous stasis of the liver, which is a conspicuous feature of canine anaphylaxis, because this rise in blood sugar can be simulated in the normal nonsensitized dog by mechanically constricting the hepatic veins for a brief interval.

The conclusion is made that there are two factors responsible for the hyperglycemia associated with anaphylaxis: (1) Sympathetic stimulation by way of the splanchnic nerves, involving the activity of the adrenals, and (2) glycogenolysis, resulting directly from venous stasis of the liver.

The Form of the Action Potential Wave in Nerve.—W. R. Amberson and A. C. Downing (from the Department of Physiology, University of Pennsylvania). We have confirmed the observation of Zotterman (*J. Physiol.*, 1928, **66**, 181) that the electric response, produced by two action potential waves in close succession, does not reach a full doubling of that given by a single wave unless the time interval between the waves is greater than 50 sigma. We secure full doubling of the response, as measured by the maximal deflection of a highly sensitive Downing moving-magnet galvanometer, only when the stimulus interval is greater than 100 sigma, at temperatures above 15° C., or greater than 150 sigma at lower temperatures.

The explanation of this long delay in recovery of the electrical properties has, we believe, been secured in a study of photographic records of the form of the galvanometer deflection produced by a single action potential wave, or by two waves in close succession. In a freshly excised nerve the form of the deflection given by the single nerve impulse differs radically from that produced by a break induction shock. When the nerve is in air, and above 15° C., this difference consists (1) in a prolongation of the time necessary for maximal deflection, indicating a persistence of "negativity" for at least 100 sigma, and (2) in a later swing to the other side of the physical zero, indicating a more delayed development of an "after-positivity," which may continue for several seconds. These persistent elements of the action potential wave are of such low voltage that they can give almost no evidence of their existence in records taken with more rapidly moving but relatively insensi-

tive instruments, such as the string galvanometer or the various oscillographs. They persist for such a time, however, that their total electrical discharge may be considerably greater than that given by the well-known initial electrical discharge at high voltage. We believe that interference between the second action potential wave and these persistent remnants of the first is responsible for the long delay in recovery observed in our earlier experiments.

The character of these persistent potentials is easily modified by various factors. After long inactivity of the nerve they tend to disappear, so that finally the deflection given by the action potential wave may be almost identical with that given by a break induction shock. They reappear when the tissue is repeatedly stimulated and become the more evident, the greater the preceding activity. In air, and above 15° C. the "after-positivity" is always present, but this element of the action potential wave completely disappears upon the application of low tensions of CO_2 or of expired air. In such an atmosphere the persistence of negativity becomes very marked; in the extreme case we have seen it endure for thirty seconds.

By curve analysis altogether similar to that which is used in modern myothermic studies the time relations of the potentials producing the deflections can be approximately determined. Our evidence indicates that, when two or more impulses follow each other at short intervals, these persistent E. M. F.'s may be partially summated. Their intervention in central nervous phenomena, therefore, seems possible. Their easy and rapid modification by changes in conditions which at least simulate physioiogic states suggests that they may have functional significance.

The Effect of Valence on Cellular Permeability to Water.—Baldwin Lucké and Morton McCutcheon (from the Laboratory of Pathology, University of Pennsylvania). When a cell, such as the egg of the sea urchin, is placed in a solution hypotonic with respect to its natural medium water enters under the driving force of osmotic pressure and the cell swells. The rate of entrance of water, per unit of time, per unit of surface, and per unit of pressure may be defined as the permeability of the cell to water, and depends on a number of factors such as temperature and composition of the medium (*J. Gen. Physiol.*, 1928, **12**, 129). In the case of the spherical egg of the sea urchin, Arbacia punctulata, the osmotic swelling proceeds relatively slowly and permits accurate measurements of the diameter, from which volume and surface of the cells can be calculated.

In the present experiments the cells were placed in hypotonic solution of dextrose to which had been added the salt to be tested. Two series of experiments were undertaken: One with a group of cobaltamine chlorides, in which the valence of the cation ranged from 1 to 6, and one with potassium salts in which the valence of the anion ranged from 1 to 4, or 1 to 3, respectively. It was found that permeability to water is regulated, at least in part, by the sign and the number of changes on the ions in the medium, in the sense that cations decrease and anions increase permeability to water; and these effects increase rapidly with the valence of the ion. It was further shown that it is possible to

determine the concentration of a cation which will oppose the effect of an anion in its tendency to increase permeability to water, and conversely, the restraining action of a cation on osmosis may be balanced by the proper concentration of an anion.

Water and Chlorid Balances in Pneumonia.—J. H. AUSTIN and F. W. SUNDERMAN (from the Department of Research Medicine, University of Pennsylvania). The water balance was measured before and after the crisis in a series of 5 cases of lobar pneumonia by means of daily weighings of the patients and weighings of ingesta and egesta. The picture is predominantly one of a negative water balance in both periods. The caloric intake was small, especially before the crisis, at which time there was a daily negative nitrogen balance from 10 to 20 gm. If the performed water from metabolized tissues and the water of oxidation from these tissues are considered in connection with the water balance then there would appear to be a tendency toward increase in the percentile water content of the tissues before the crisis and a decrease following the crisis.

Our chloride-balance studies may be divided into two groups: the first consisting of 4 patients under the ordinary régime in which the daily chloride intake averaged between 1 and 1.5 gm. NaCl; and the second consisting of 3 patients receiving from 15 to 30 gm. NaCl daily before the crisis. The first group excreted more salt than they ingested during the precritical period, whereas the opposite occurred in the second group. The precritical low Cl excretion in our pneumonia patients was a consequence of the low Cl intake and under the ordinary régime the Cl balances were negative rather than positive.

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